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Hepatitis B in Oman

risk factors and sequelae

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ABSTRACT

Background

Hepatitis B is a major public health problem worldwide. The prevalence of hepatitis B is dependent on the modes in which it is transmitted. There are two common modes of hepatitis B virus (HBV) spread: vertical (mother to neonate) and the horizontal (via infected blood or body fluids). Chronic infection with HBV can progress to liver cirrhosis and liver cancer (hepatocellular carcinoma; HCC). Oman is regarded as an intermediate endemicity region and has had neonatal vaccine against HBV since 1990; however, little research has been conducted in Oman regarding risk factors for hepatitis B and its contribution to end stage liver disease and HCC.

Aims

- To identify the prevalence of major risk factors for acquiring hepatitis B in Omani patients currently infected with HBV (positive hepatitis B surface antigen (HBsAg)).
- To estimate the contribution of hepatitis B to liver cirrhosis in Oman.

Methods

The prevalence of major risk factors was identified by interviewing HBsAg positive patients using a standard questionnaire. Patients were recruited from outpatient clinics at two tertiary referral hospitals in Oman's capital city Muscat.

Data on patients with liver cirrhosis admitted to two tertiary hospitals in Muscat over a period of seven years was abstracted from medical records. The diagnosis of cirrhosis was confirmed using defined criteria and the aetiology confirmed from the results of diagnostic tests including HBV serology. This data was analysed to estimate the contribution of HBV to cirrhosis in the cohort.

Results

For the first objective, 279 patients were interviewed. The number of male and female patients was similar, and 75.5% of the participants were aged 20 – 39 years. Antenatal screening was the most common means of detecting HBV infection in women and prior to blood donation was the most common means of identifying HBV infection in men. With respect to HBV transmission risk factors, intra-familial contact with HBV infected persons

and behavioural risks such as body piercing (females) and barber shaving (males) were more common than nosocomial risk factors. Knowledge about HBV infection was scarce among our participants.

For the second objective, we identified records from 419 patients with cirrhosis. The median age was 59 years and males accounted for two thirds of the total studied population. 97.1% of patients were of Omani ethnicity. There was evidence of previous or current HBV infection (positive anti-bodies to hepatitis B core antigen) in 51.3% of the cirrhotic patients. 21.5% had active HBV (positive HBsAg). Of the patients with current HBV 91.2% were infected with HBV alone while 8.8% were co-infected with hepatitis C virus (HCV). Hepatitis C was present in 30.5% of cirrhotic patients and nearly half of those patients had evidence of past exposure to HBV. When stratified by gender, HBV infection was more common among male cirrhotic patients compared to females.

Conclusions

This study found that risk factors for HBV infection in Omani patients include direct contact of infected individuals within a family and exposure to high-risk behaviours such as piercing and barber shaving. Reducing vertical and horizontal transmission of hepatitis B in Oman could be improved by the implementation of routine antenatal screening of pregnant women and a greater focus on contact screening respectively. Future work is required to determine whether the association with behavioural risk factors is causal, particularly piercing and shaving at barber shops. If confirmed, relatively simple and effective interventions could be developed to reduce the risk of horizontal transmission related to these activities.

We found that third of the patients identified with liver cirrhosis had past exposure to HBV and 20% had evidence of chronic infection. Most patients were of older age and male sex. This group of patients may benefit from antiviral therapy to prevent decompensation and regular surveillance for early diagnosis and treatment of HCC. Further research is required to assess the role of other exposures (alcohol, co-infection with other viruses) in the prognosis of hepatitis B to cirrhosis in Oman.

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LIST OF ABBREVIATIONS

HBV: hepatitis B virus/infection

CHB: chronic hepatitis B

AHB: acute hepatitis B

ORF: open reading frames

HBsAg: hepatitis B surface antigen

Anti-HBs: anti body to hepatitis B surface antigen

HBcAg: hepatitis B core antigen

Anti-HBc: anti body to hepatitis B core antigen

HBeAg: hepatitis B envelope antigen

Anti-HBe: anti body to hepatitis B envelope antigen

HBV DNA: hepatitis B virus deoxyribonucleic acid

ALT: alanine aminotransferase

AST: aspartate aminotransferase

HCV: hepatitis C virus

HDV: hepatitis D virus

HIV: Human Immunodeficiency Virus

HCC: hepatocellular carcinoma

IDU: intravenous drug use

US: ultrasonography

CT: computed tomography

MRI: magnetic resonance imaging

WHO: World Health Organisation

MoH: Ministry of Health

CDSC: Communicable Diseases Surveillance and Control

SQUH: Sultan Qaboos University Hospital

AFH: Armed Forces Hospital

GCC: Gulf Cooperation Council

α -IF : alpha interferon

NUCs: Nucleos(t)ide Analogues

AFP: alpha-fetoprotein

1. CHAPTER ONE: INTRODUCTION

This thesis reports on the studies to investigate aspects of the epidemiology of hepatitis B in Oman. There is currently little work in this area in Oman. Hepatitis B is an inflammation of the liver caused by the hepatitis B virus (HBV) and is a major global health problem. Almost 2 billion people, that is 30% of the world's population, have been infected with HBV and 350 million are chronic carriers (Lavanchy, 2004). More than 75% of HBV cases are found in Asia, the Middle East and Africa (Andre, 2000). Oman is considered to be a country of intermediate endemicity for hepatitis B with 2-7% of the population being infected (Al-Naamani et al., 2013). The hepatitis B vaccine was introduced to the Expanded Program on Immunization in 1990 with a reported coverage percentage of more than 98% for children less than one year of age in the year of 2012 (Sultanate of Oman Ministry of Health, 2012)

HBV is mainly transmitted via blood and body fluid. There are two main modes by which HBV transmission occurs, vertical and horizontal. HBV transmission risk factors show substantial variation globally. Vertical transmission, i.e. from mother to child is the most common mode of transmission in high endemicity regions, which is responsible for most cases of chronic hepatitis B. Early horizontal transmission of HBV in children under the age of 5 years is thought to be the principal mode of transmission in the Middle East (Toukan, 1990). Other common modes of transmission (late horizontal transmission) include unsafe medical settings, sexual contact (heterosexual or homosexual) and intravenous drug use (IDU) (World Health Organization, 2002). Those mechanisms of spread are more common in low prevalence areas.

According to the World Health Organisation, around 600,000 people die each year from hepatitis B related liver disease. More than 75% of HCC and liver cirrhosis cases in the Eastern Mediterranean Region are attributed to hepatitis B and hepatitis C infections (Perz et al., 2006).

The thesis initially consisted of three main objectives. These were; (1) to estimate the incidence of acute hepatitis B (AHB) in Oman, (2) to identify the prevalence of major risk factors for acquiring HBV in Omani HBV positive patients and (3) to estimate the contribution of HBV to liver cirrhosis and HCC in Oman. The first objective was to be initially achieved using data derived from reported cases of AHB in Oman and the published literature. However, this is likely to underestimate the real incidence and is discussed in

chapter three (see 3.4). Therefore I decided to abandon the first objective.. In relation to objective three, although HCC develops more commonly in patients with cirrhosis, patients with chronic hepatitis B (CHB) are at risk of developing HCC even in the absence of underlying cirrhosis. We initially aimed to investigate the role of HBV in both cirrhosis and HCC in Oman. However, there was another study being conducted to look at HCC and its aetiologies at the same time as I was conducting my study. Hence, objective three estimated the contribution of HBV to liver cirrhosis only.

1.1 Overview of the thesis

The remainder of this thesis consists of five chapters. Each chapter will look at the following;

- CHAPTER 2 contains background information about Oman, the clinical features of hepatitis B and available preventive strategies.
- CHAPTER 3 provides information derived from the literature regarding the epidemiology of hepatitis B, risk factors for the transmission of HBV and the current status of hepatitis B in Oman.
- CHAPTER 4 investigates, in a cross sectional study, the prevalence of major risk factors for acquiring of HBV in Omani patients positive for HBsAg.
- CHAPTER 5 attempts to estimate the contribution of HBV to liver cirrhosis in Oman by conducting a cross sectional study of medical records.
- CHAPTER 6 summarizes the main findings of this research and lists the implications of these findings.

2 BACKGROUND, CLINICAL FEATURES AND PREVENTION OF HEPATITIS B

2.1 Oman and health services

The Sultanate of Oman is located in the southeast of the Arabian Peninsula. It is bordered by The Republic of Yemen to the southwest, the Kingdom of Saudi Arabia to the west and the United Arab Emirates to the north. Oman has an area of 309,500 square kilometers and a total population of 2,773,479 people of which 1,957,336 are Omanis and 816,143 are expatriates. Muscat is the capital city of Oman and it embraces about 28% of total population. The remainder are distributed between Al Batinah, Al Sharqiyah, Al Dakhliyah, and Dhofar (28%, 13%, 12% and 9% respectively) (figure 2.1). Oman has a young population with 55% of the population under the age of 19 (General Census of Population Housing & Establishments 2010, 2010). The official language is Arabic and Islam is the official religion.

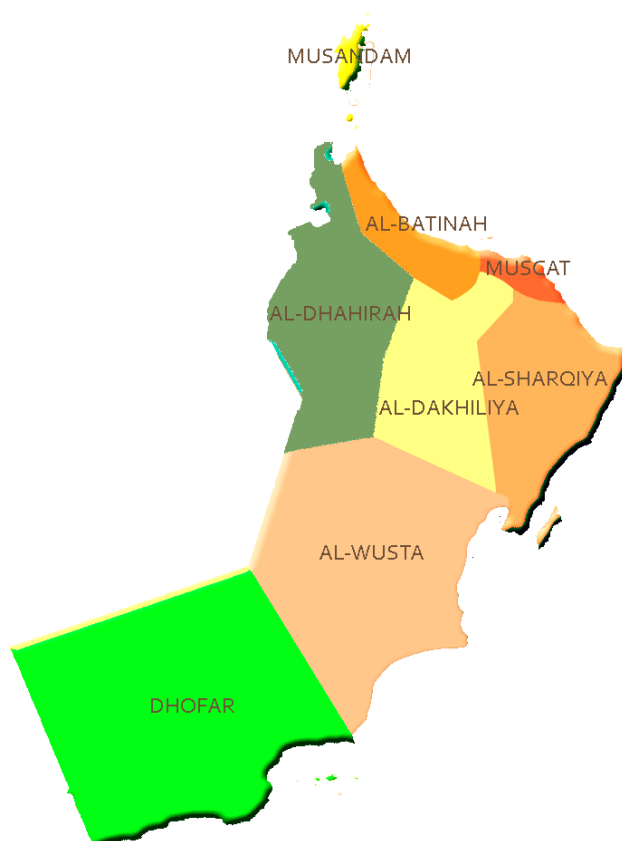


Figure 2.1 Map of the Sultanate of Oman

Reference: http://omanpocketguide.com/index.php?option=com_content&task=view&id=58&Itemid=72

The World Bank classifies Oman as a high-income economy with an annual per capita national income of \$12,476 or more. Before the year of 1970, there were only three schools in Oman with 909 students of whom all were males. However, under the ruling of His Majesty Sultan Qaboos Bin Said, the government has invested in the educational sector to form a strong educational infrastructure. The illiteracy rate of people above the age of 15 has decreased from 41% in 1993 to 22% in 2003 (General Census of Population Housing & Establishments 2010, 2010).

There has been an incredible advancement in the health sector in Oman with an increase of the number of hospitals from two with 12 beds and 10 clinics in 1970 to more than 50 hospitals and 176 health centres run by the MoH distributed around the Sultanate by the year of 2010 (Sultanate of Oman Ministry of Health, 2010). Health care services are easily accessible and free of charge for all Omanis.

The MoH is the main provider of health services in Oman. However, there are other health providers run by Ministry of Defence, Royal Oman Police (ROP), Petroleum Development Oman (PDO) and Sultan Qaboos University (SQU). Health services in Oman are available in two forms; hospitals and health centres. Hospitals include Governorate Hospitals that provide secondary and tertiary referrals, and Wilayat Hospitals that provide primary and secondary health services. Health centres on the other hand provide only primary outpatient services. All of these institutions serve people within their catchment area. The Muscat Governorate has more regional hospitals than any other region in Oman and they act as the national referral hospitals for cases from other regional hospitals.

In the year of 2011, a total of 3,267,541 outpatient visits (including HBV cases) were made to regional hospitals, 46% of them were to health services other than MoH. The latter visits were mainly to the Armed Forces Hospital (AFH) and Sultan Qaboos University Hospital (SQUH) (49.7% vs 19.5% respectively) (Sultanate of Oman Ministry of Health, 2011).

The AFH and SQUH are major regional hospitals in Muscat that provide secondary and tertiary health services to their employees and dependents. In addition, the SQUH provides care for the general population. The AFH serves more than one third of the Omani population from different geographical regions (Al-Naamani et al., 2013).

2.2 Hepatitis B virus

2.2.1 Structure

The hepatitis B virus is classified within the family of hepadnavirus which solely infect hepatocytes. It is an enveloped virus measuring 42nm in diameter. The virus consists of 27nm isometric core and is surrounded by an outer coat of 4nm thickness. HBV contains a partially double stranded, circular 3.2 kb DNA genome consisting of four partly overlapping open reading frames (ORFs). ORF C encodes for the HBV core antigen and envelope antigen (HBcAg and HBeAg). ORF P encodes for the reverse transcriptase enzyme polymerase. ORF S encodes for the three forms of the HBsAg envelope protein (small, middle and large). Finally ORF X encodes for a transcriptional trans-activator protein needed for viral replication (Kramvis et al., 2005) (Neuveut et al., 2010).

2.2.2 Genotypes

There are 8 genotypes of HBV identified (A-H). The 8 genotypes differ in their length of open reading frames and the size of protein products translated.

HBV genotypes have different geographical distributions. Genotype A is found mostly in North America, Northeast Europe and Africa. Genotypes B and C are mostly found in Asia and Oceania. Genotype D is found worldwide but predominantly in the Mediterranean region including Oman. Genotype E is most commonly found in the Western Coast of Africa and Madagascar on the East. Genotype F is found in aboriginal populations of South America. Genotype G is mainly found in France, Germany, United Kingdom, Italy and the United States of America. Lastly, genotype H is predominantly found in Amerindian populations of Central America, California and Mexico. There is also geographical variation in the distribution of HBV genotypes within countries such as in China, India and USA (Kramvis et al., 2005).

It has been suggested that the different genotypes of HBV may have an effect on the progress of HBV related diseases. Studies found that genotype B is associated with less aggressive clinical course, early seroconversion of HBeAg with more sustained remission, decreased activity of necroinflammation in the liver, a slower rate of progression to cirrhosis and development of HCC compared to genotype C (Lok and McMahon, 2007, Lesmana et al., 2006). In Japanese patients, genotype A has the highest chronicity rate compared to genotypes B and C (Yotsuyanagi et al., 2012). In India, genotype D is associated with more severe liver disease than genotype A ($p < 0.05$) (Thakur et al., 2002).

The structural and functional differences between HBV genotypes may influence the response to treatment. When treated with interferon-alpha (IFN- α), genotypes A and B are associated with higher rate of HBeAg seroconversion compared to genotypes C and D (Lok and McMahon, 2007). Moreover, genotype C is thought to increase resistance to interferon therapy (Lesmana et al., 2006).

2.3 Clinical Aspects of hepatitis B

2.3.1 Clinical sequence of acute hepatitis B:

This section is mostly based on a paper by Mitchell L. Shifman unless indicated otherwise. Development of acute hepatitis B is dependent on the age of infection and mode of transmission. Persons acquiring the infection perinatally are less likely to manifest acute infection compared to those acquiring the infection during adulthood (1% vs. 95% likelihood) (Goldstein et al., 2005).

The human body can be susceptible to HBV transmission by either percutaneous or permucosal exposure. Percutaneous transmissions of HBV include transfusion of infected blood or blood products, organ transplant, use of contaminated needles, haemodialysis, cuts and playground injuries in childhood, tattooing and acupuncture. On the other hand, permucosal transmission of HBV results from homo/heterosexual activity and perinatal exposure (World Health Organization, 2002).

Following the exposure, the virus circulates in the blood stream until it reaches the liver. The virus then enters hepatocytes by an unclear mechanism. The virus will then replicate in the hepatocytes leading to an increase in serum HBV DNA levels, and the expression of HBV proteins in the surface of infected hepatocytes (Shiffman, 2010). As a result, the immune response is initiated against the infected hepatocytes causing them injury. This is known as the incubation period where patients are usually asymptomatic with normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. This period lasts for an average of 60 days; however, it may vary depending on the size of HBV inoculum, ability of antibodies to capture HBV, genetic variations and mode of transmission. At this stage, the serological markers appearing in the host's serum are HBV DNA, HBsAg and HBeAg.

The next period is the prodrome. At this stage, the levels of aminotransferases are elevated. The clinical presentation of patients in this period differs according to the age and immune status of the host. Infants, children and immune suppressed individuals are often completely

asymptomatic. On the other hand, adults develop non-specific symptoms such as malaise, anorexia, nausea, vomiting and abdominal pain. Such symptoms may last for a very short time of only 1-5 days and the diagnosis of HBV infection can be missed easily. Anti-HBc, HBsAg and HBeAg appear at this stage.

The next phase is the icteric phase. This is defined as the onset of jaundice (bilirubin > 10 mg/dL) approximately 90 days after infection. It is associated with appearance of dark urine, followed by pale stools and yellowish discoloration of the mucous membranes, conjunctivae, sclera and skin. It is important to note that not all acutely infected patients with HBV develop the icteric phase and it is mainly dependent on the age of infection. The risk of developing jaundice is 1%, 10% and 40% in neonates, children and adults respectively (figure 2.2). This stage lasts for 4-12 weeks and is the stage where most cases seek medical care. Anicteric AHB is common in patients with human immunodeficiency virus (HIV), chronic renal failure on dialysis and patients with diabetes mellitus

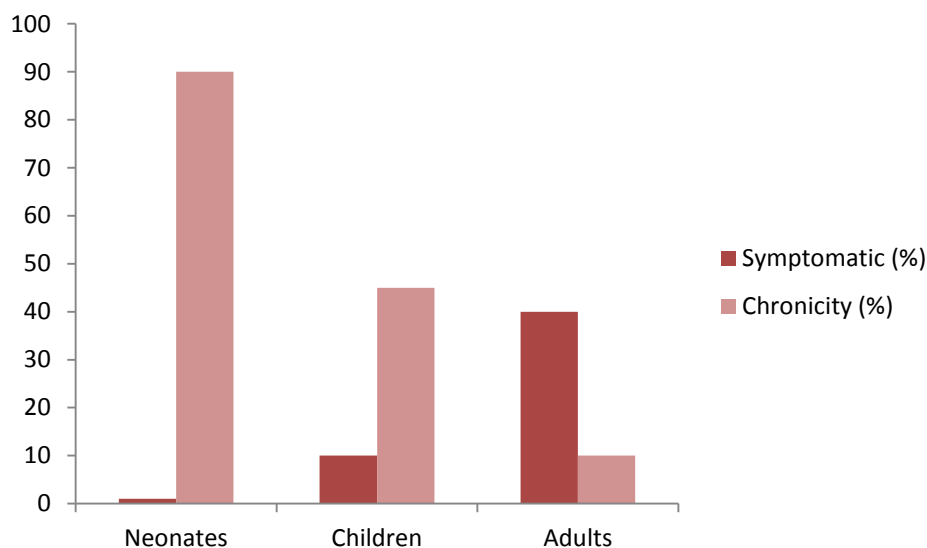


Figure 2.2 Relationship between the development of symptomatic acute icteric hepatitis, age and the likelihood of developing chronic HBV.

Reference: (Shiffman, 2010)

The last phase is the resolution stage. This stage is associated with a decrease in AST and ALT levels. It is also associated with disappearance of symptoms which is dependent on their severity. Patients who develop mild non-specific symptoms usually clear symptoms within few days, while those who develop acute jaundice, take weeks or months to clear the symptoms. Moreover, elimination of HBV DNA and seroconversion to anti-HBs, anti-HBe and anti-HBc IgG, (the latter lasts for a life time) occur in this stage. However, this is

dependent on the age and severity of the infection. Complete resolution is achieved in those with a short incubation period and who develop symptoms and jaundice. On the other hand, asymptomatic patients usually proceed to chronic infection.

2.3.2 Natural history of chronic hepatitis B

Information in this section is derived from two review articles by Fattovich et al and Neuveut et al (Fattovich et al., 2008) (Neuveut et al., 2010). CHB is defined as the failure to achieve seroconversion of HBsAg six months after infection with HBV. It occurs in 90%, 50% and 10% of patients infected during infancy, early childhood and adulthood respectively.

There are five phases of CHB; the immune tolerance phase, the immune active phase, the inactive HBV carrier phase, the HBeAg negative CHB and finally the HBsAg negative phase.

The first stage is the immune tolerant phase. This stage is associated with positivity of HBeAg, raised levels of HBV DNA with normal or minimally elevated ALT. On histology, minimal liver damage is seen. This phase lasts for 1 to 3 decades in patients infected during infancy; however, it is much shorter in patients infected during childhood or adulthood.

The second stage is the immune active, immune clearance or CHB phase. At this stage, immune cells attack infected hepatocytes. This leads to rise in serum ALT levels and continuous fall in HBV DNA levels. Moderate to severe liver necroinflammation is noted on liver histology which may progress to fibrosis. Senescent hepatocytes are frequently found in patients at this stage of CHB which is believed to protect against malignancy. Patients presenting at this stage are usually infected during adulthood.

The third phase is known as the inactive HBV carrier phase. At this stage seroconversion to HBeAg negative, anti-HBe positive is achieved. It is also characterized by normalization of ALT levels, low or undetected levels of HBV DNA and histological improvement of fibrosis and inflammation.

The fourth phase is the reactivation phase (or, as in most cases, HBeAg negative chronic hepatitis B). Almost a third of patients from the previous stage will move into this stage. This is due to reactivation of HBV DNA by either spontaneous or immune suppression mechanisms. As a result, patients may return to the HBeAg positive state by reactivation of a wild type virus, or more commonly, reactivation of replication HBV variants that hinder the expression of HBeAg. Clinically, patients will have fluctuating levels of HBV DNA and ALT. On histology, active hepatitis with a variable amount of fibrosis is noted.

The final stage in the natural history of CHB is HBsAg negative stage. Only a small number of chronically infected patients (2% annually) will be able to lose the HBsAg and develop anti-HBs. This stage is associated with favourable prognosis of the disease. However, low levels of HBV DNA will remain detectable by PCR or liver biopsy. These patients will remain at risk of reactivation of hepatitis B whenever immunosuppressed.

Table 2.1 Natural history of CHB

HBeAg status	HBeAg positive		HBeAg negative		
Stage of chronic infection	Immune tolerant phase	Immune active or CHB phase	Inactive HBV carrier phase	HBeAg negative chronic hepatitis B	HBsAg negative phase
HBV DNA	Raised serum HBV DNA	Low serum HBV DNA	Low serum HBV DNA	Fluctuating levels of HBV DNA	Very low serum HBV
ALT	Normal serum ALT	Raised serum ALT	Normal serum ALT	Fluctuating levels of serum ALT	Normal
Liver histology	Minimal liver damage	Moderate to severe liver necroinflammation	Improvement of fibrosis and inflammation	Active hepatitis with variable degree of fibrosis	Improvement in histology

Note: data from (Neuveut et al., 2010)

2.3.3 Diagnosis of HBV infection

Serologically, the presence of HBsAg and anti-HBc class IgM indicates acute infection with HBV. On the other hand, chronic infection is diagnosed by the presence of HBsAg or by HBV DNA and anti-HBc class IgG for more than six months. The sole presence of anti-HBs indicates successful vaccination, whereas when accompanied with positive anti-HBc, it indicates immunity due to previous infection.

Sometimes, an isolated anti-HBc is found in the blood (Lok and McMahon, 2007). This may be indicative of CHB where HBsAg has decreased to undetectable levels. This is common in high endemicity regions and in HBV patients co-infected with HIV or HCV. However, HBV DNA will remain detectable in liver. It can also be indicative of immunity where anti-HBs have fallen to undetectable levels, but anamnestic response can be observed after one dose of the vaccine in those patients. Another explanation is false positivity of anti-HBc. This is

common in individuals from low endemicity regions; however, they will respond to the vaccine similarly to those with no other HBV markers. Finally, during the window phase in acute hepatitis B, only anti-HBc is present in the serum but it should be of class IgM.

2.3.4 Management of Hepatitis B

Not all HBV positive patients require treatment. AHB is usually self-limiting and hence not treated with antiviral therapy. Patients with CHB on the other hand, are evaluated initially to decide on the appropriate treatment plan. Those with normal ALT respond poorly to current medicines and, therefore, are not considered for treatment. However, it is recommended that they have regular follow-up every 6 or 12 months to detect any changes in the disease status (Mohamed et al., 2004).

Chronically infected patients with elevated ALT levels are treated to achieve suppression of HBV replication and remission of liver disease. The ideal aim is to prevent progression of the disease to cirrhosis, hepatic failure and HCC. Success of the treatment is evaluated by normalization of serum ALT, decrease in viral load (HBV DNA), loss of HBeAg with or without seroconversion to anti-HBe and histological improvement of the liver (Lok and McMahon, 2007).

Antiviral therapies currently approved to treat hepatitis B are available in two forms; alpha interferon (α -IF) and Nucleos(t)ide Analogues (NUCs). Conventional α -IF is one of the drugs that are commonly used to treat chronic hepatitis B. It has a dual action of modulating the immune response and inhibiting the replication of HBV (Lavanchy, 2004). However, α -IF is associated with undesirable side effects, the painful route of administration of three weekly injections and high cost. The first NUC to become widely available is lamivudine. NUCs have the advantages of oral administration, reduced side effects and lower costs. However, resistance can develop with long-term treatment of more than 6-9 months, which limits the use of this NUC agent (Lavanchy, 2004). Subsequently a number of other NUCs have been developed to overcome the problem of resistance, and many of those are now available and approved for use (2012b).

2.3.5 Progression to cirrhosis and HCC

According to WHO, around 600,000 people die each year from hepatitis B related liver disease (Perz et al., 2006). HBV infection severity ranges from acute hepatitis with recovery and clearance of the virus from the host's body, to progressive chronic disease leading to

cirrhosis of the liver and/or primary liver cancer. Annually, 2-3% of chronic HBV carriers develop cirrhosis with a further 3% progressing to decompensated cirrhosis (Chen et al., 2007). CHB is the major cause of HCC worldwide with more than half of HCC patients being chronic carriers. The risk of developing HCC in HBsAg patients is estimated to be 25-37 times higher than non-infected people (Neuveut et al., 2010), with a 20% to 25% life time risk of death from HCC (Chen et al., 2007)

There are several factors that are known to have a significant impact on the progression to cirrhosis and HCC. These include host, viral, clinical, lifestyle and environmental factors. The summary below is mainly derived from two review articles by Fattovich et al and McClune & Tong (Fattovich et al., 2008) (McClune and Tong, 2010).

2.3.5.1 Host factors:

Host dependent factors that influence the clinical outcome of CHB include age, gender and other factors such as region of origin and family history of HCC. Studies conducted in Asia and Western countries showed that the incidence of developing cirrhosis in HBV infected individuals increased significantly with increase in age, particularly over the age of 40 years. This can be attributed to the longer duration of disease exposure (Fattovich et al., 2008). As for developing HCC, cohort studies showed that patients aged 40-49 years are 3.6 to 5.4 times more likely to develop HCC compared to younger patients (McClune and Tong, 2010). This risk increased to 8.3-17.7 in patients above the age of 60 years.

Male gender is found to be an independent risk factor for cirrhosis. It is suggested that the antifibrogenic effect of oestrogen inhibits the activation of stellate cells and hence reduces the process of fibrosis (Fattovich et al., 2008). Male gender was also found to be a risk for developing HCC with an adjusted relative risk (ARR) of 2.1 (95 CI 1.3-3.3) and 3.6 (95% CI 2.4-5.3) in men compared to women (McClune and Tong, 2010). Studies showed that the incidence of HCC in CHB patients per 100,000 person-years was almost three times higher in males in Taiwan, and up to five times higher in males in the USA (Nguyen et al., 2009).

Studies from Eastern and Western regions show major differences in the incidence of cirrhosis and HCC. In high endemic regions such as Asia, HBV accounts for 70% of HCC cases (except for Japan 11%) (McClune and Tong, 2010). In low endemicity regions with increased numbers of immigrants from Asia, 70% to 80% of HBV induced HCC patients are of Asian ethnicity (Nguyen et al., 2009). In the USA, Asians develop HCC at a rate two times that of African Americans and four times that of Caucasians (McClune and Tong, 2010).

Individuals with a family history of HCC are more likely to progress to HCC from hepatitis B. This is noticed more in first degree relatives especially siblings (McClune and Tong, 2010). This could be related to exposure. It may also suggest a role of genetic predisposition which is still under study (Fattovich et al., 2008).

2.3.5.2 Hepatitis B Viral Factors

HBeAg

The risk of developing cirrhosis in patients with HBeAg positive chronic hepatitis ranges from 0.5 per 100 person years in immune tolerant patients with normal ALT levels to 3 per 100 persons years in immune clearance patients with elevated ALT levels (Fattovich et al., 2008). This is because patients in the immune tolerance phase have minimal or no liver damage and fibrosis; however, progression to the immune active phase is associated with moderate to severe liver necroinflammation and hence increased rate of fibrosis (Fattovich et al., 2008) (Neuveut et al., 2010).

Patients with HBeAg negative chronic hepatitis were found to have almost two times the risk of developing cirrhosis of those with positive HBeAg status. This is because HBeAg seroconversion occurs at a later stage in the natural history of CHB; therefore, patients with HBeAg negativity had a longer duration of the infection (Fattovich et al., 2008). Moreover, HBeAg negative chronic hepatitis is associated with mutations in the pre-core and basal core promoter regions of the HBV genome which prevent the expression of circular HBeAg and increase the risk for cirrhosis and HCC (Neuveut et al., 2010).

HBV DNA

Increased levels of viral load were one of the strongest independent predictors of cirrhosis development and an independent predictor of HCC even after adjusting for known co-variants (Chen et al., 2007). Participants with HBV DNA levels between 300 and less than 10,000 copies/mL were two times more likely to progress to cirrhosis compared with those who had HBV DNA levels below 300 copies/mL. Overall, HBV DNA of more than 10,000 copies/mL was associated with significant increased risk for progression to cirrhosis and development of HCC.

Genotypes

HBV genotypes affect the outcome of the HBV infection differently. For instance, genotype C is associated with a lower rate of spontaneous HBeAg seroconversion, hence prolonging HBV replication duration. This is associated with more severe hepatitis activity which may increase the risk of cirrhosis compared to those with genotype B (Fattovich et al., 2008). However, genotype B is found to be associated with earlier development of HCC in patients younger than 50 years and those who are not cirrhotic (Kao* et al., 2000). Genotype D is more prevalent in subjects with cirrhosis, suggesting more severe liver diseases and subsequent development of HCC (McClune and Tong, 2010).

2.3.5.3 Clinical factors:

Co- infections with other viruses affect the progression of CHB to cirrhosis or HCC. In addition, established cirrhosis increases the risk of HCC development.

Hepatitis C virus (HCV) co-infection

Dual infection of HBV and HCV alters the prognosis of the disease. This situation is not uncommon as it has been estimated that 10-15% of CHB patients are co-infected with HCV (Fattovich et al., 2008). This is, as expected, more noted in areas with high prevalence of HCV and HBV infections. One cohort study from Taiwan found a significant association between developing cirrhosis and dual infection of HBV and HCV (Liaw et al., 2004). CHB patients who get acute HCV superinfection were 3.3 times more likely to develop cirrhosis than those infected with HBV alone.

Studies conducted in Western and East Asian regions demonstrated an increase in the risk of developing HCC in patients with dual HBV and HCV infection compared to those with only HBV infection by 2-fold (Fattovich et al., 2008).

Hepatitis D virus (HDV) co-infection

HDV co-infection also impacts the outcome of HBV infection. It is estimated that 5% of HBV carriers worldwide are co-infected with HDV, which is more common in South America and the Mediterranean basin (Fattovich et al., 2008).

Patients who are infected with both HBV and HDV had a roughly 3-fold increased risk of developing cirrhosis and HCC compared to those infected with HBV alone.

Human Immunodeficiency virus (HIV) co-infection

The prevalence of HBV infection among HIV infected people ranges from 5-30% with it being more prevalent in Asia and parts of sub-Saharan Africa (Fattovich et al., 2008). The risk of chronic hepatitis B carriage increases in patients with HIV (Rockstroh, 2003). Moreover, HBV and HIV co-infection is associated with higher HBV replicative activity and lower rate of spontaneous HBeAg seroconversion. As a result, progression to cirrhosis is accelerated and the rate of decompensated cirrhosis is raised; however, the rate of HCC is not affected (Fattovich et al., 2008).

Cirrhosis

The risk of developing HCC is higher in cirrhotic patients regardless of their geographical origin. This risk increases in people infected with HBV from Asia rather than from Western countries (Fattovich et al., 2008). This can be attributed to the acquisition of the infection at a younger age and hence the longer time of infection. Around 90% of HBV induced HCC have histologic evidence of cirrhosis (McClune and Tong, 2010).

2.3.5.4 Lifestyle factors:

Alcohol and Smoking

Alcohol is a major factor and co-factor for the development of cirrhosis and HCC. When combined with HBV infection, the natural course of the disease is affected negatively. A study conducted in Japan found that HBV infected patients with history of alcohol intake of $\geq 500\text{Kg}$ are 6.4 and 8.37 times more likely to develop cirrhosis and HCC respectively than those with alcohol intake history of $< 500\text{Kg}$ (Ikeda et al., 1998) (the calculation method of 500kg alcohol history was not reported in the study, but it was assumed to reflect high alcohol consumption). In addition, the presence of anti-HBc alone with negative HBsAg status in patients with alcoholic cirrhosis was significantly associated with a more severe clinical profile like jaundice, high values of bilirubin, prothrombin time (PT) and Model for End-Stage Liver Disease (MELD) score (Zhang, 2013). Moreover, anti-HBc was associated with higher risk for short-term mortality.

Studies conducted in Taiwan showed conflicting results on the role of cigarette smoking on the outcome of CHB. A 1.5 fold increased risk for HCC in smokers compared to non-smokers was found in one study while zero impact was reported when studying a larger population size (McClune and Tong, 2010).

Metabolic Factors

Diabetes is considered an independent risk factor for the development of HCC regardless of the presence of HCV, HBV, alcoholic liver disease or cirrhosis (McClune and Tong, 2010). Similarly, BMI of 35-40 increases the mortality risk by 5-fold in HCC patients compared to normal BMI (McClune and Tong, 2010).

2.3.5.5 Environmental risk factors:

One of the environmental risk factors that increases the risk of HCC is aflatoxin. Aflatoxin is a carcinogen that affects the liver by ingestion of mouldy foods resulting from storage of various grains most commonly in sub-Saharan Africa and Southeast Asia (Montesano, 2011). It has been shown that the risk of HCC rises by 3-fold in males modestly exposed to aflatoxin (McClune and Tong, 2010).

Table 2.2 Summary of the factors that affect the prognosis of CHB

Factors associated with increased risk of HBV related cirrhosis and HCC	
Host	Male gender, age>40 yrs, Asian ethnicity, positive family history
HBV	HBeAg negative CHB, HBV DNA> 10,000 copies/ mL, genotypes C and D.
Clinical	Co-infection with HCV, HDV or HIV, cirrhosis.
Lifestyle	Alcohol, metabolic syndrome.
Environmental	Aflatoxins

2.4 Prevention of Hepatitis B

2.4.1 Hepatitis B vaccine

WHO recommended in 1992 that all countries should vaccinate newborns, adolescents and high risk groups against HBV. This led 177 countries to include HBV vaccine to their universal immunization by the end of 2009. This has reduced the prevalence of HBV carrier state which is mainly associated with perinatal transmission, hence preventing the risk of developing HCC making this vaccine the world's first cancer vaccine. Taiwan was one of the first countries to initiate universal immunization against HBV in July 1984 (Chen et al., 2012). Table 2.3 shows the vaccination programs of different countries.

Table 2.3 HBV vaccination programs in different countries

Country (year of vaccine implementation)	Neo-natal vaccination schedule	Infant coverage (%)	Catch-up vaccinations, and high risk groups
Oman (1990)*	at birth 0, 3, 7 months	>95 (2005)	Adolescents in schools Healthcare workers Contacts of HBV infected individuals
Saudi Arabia (1989)^	At birth, 1, 5 months	85%	All Saudi children at school entry Health care workers Haemodialysis patients
China (1992)**	0, 1 and 6 months	70 (2001)	Pre-school children Adolescents Healthcare workers
Taiwan (1984)**	0, 1 and 6 months		Pre-school First graders All children <15 years of age
Australia (1996)**	0, 2, 4, 6 or 12 months		Adolescents High-risk groups
New Zealand (1987)**	0, 1 and 3 months	90 (2001)	Children entering high school Since 2000 an adult catch-up program targeting high-risk groups (Maori, Pacific Islanders and Asians) At risk groups

*(Sultanate of Oman Ministry of Health)

** (Mohamed et al., 2004)

^ (Abdo et al., 2012a)

Catch-up vaccination of individuals born before the introduction of neonatal vaccination is implemented in some countries around the world. These strategies are found to be more beneficial in areas of lower endemicity, i.e where infection is mainly acquired among

adolescents and adults. However, in high endemicity countries, such campaigns are not recommended as infection is chiefly transmitted perinatally or during early childhood (Mohamed et al., 2004).

Hepatitis B vaccine is safe in pregnant women at any stage of pregnancy, so pregnant women who have never been immunized against HBV and who are at risk of being infected should not be deterred from getting the three doses of vaccine. It is also safe and immunogenic in patients with mild-moderate liver disease (Yu et al., 2006) (Tran, 2012).

2.4.2 Limitations and Challenges

There are a number of limitations and challenges faced by the world in order to reach a full HBV vaccine coverage. Some of these challenges are discussed below.

2.4.2.1 Compliance

One of the challenges to effective immunization against hepatitis B is the compliance of vaccine recipients to the three-dose administered over a period of six months. In Turkey statistics suggested that 11% to 20% did not adhere to the HBV three-dose vaccine at age 0 (OZER A et al, 2011). The reasons for noncompliance include socioeconomics factors such as older age, lower household income and lower educational levels which decreases awareness about the importance of having the hepatitis B vaccine (Park et al., 2012). However, such characteristics may have different effects in developed countries. In the USA, for example, the vaccination rate is found to be lower in infants born to mothers with a higher educational level, higher annual income and private insurance (O'Leary et al., 2012).

Some have studied the use of a two-dose vaccine as an alternative which may enhance compliance to the immunization schedule. Halperin et al, for example, found while conducting a randomized observer blinded control trial that an alternative two-dose vaccine had a statistical superiority in seroprotection rate and magnitude of antibody response when compared to the three-dose licensed vaccine in 18-55 years of age (Halperin et al., 2012).

2.4.2.2 Inadequate implementation of recommended prevention strategies

Perinatal transmission of HBV is the predominant mode of transmission in high endemicity regions such as Asia and Africa which is responsible for most of the chronic cases and hence increasing the risk of developing cirrhosis and HCC. Therefore, antenatal screening of pregnant women for HBsAg is essential to identify new-borns who are at high risk of being

infected. The risk of transmission is increased by forty-fold in neonates of HBeAg positive mothers when compared to HBeAg negative mothers (Chen et al., 2012).

Today there are three main immunoprophylactic strategies against HBV implemented around the world. The first strategy is the active immunization using the three-dose hepatitis B vaccine only in all neonates. The second strategy is active immunization using the three-dose vaccine plus passive immunization by administering hepatitis B immunoglobulins (HBIG) to neonates born to HBsAg mother regardless of her HBeAg status. The third strategy is to actively and passively immunize neonates born to HBsAg and HBeAg positive mothers (Chen et al., 2012).

Studies have shown that passive immunization with a single dose of hepatitis B immune globulins within the first 12 hours of birth in addition to the active immunization with three doses of intramuscular hepatitis B vaccine within 0, 1 month and 6 months respectively, would be a 90-100% effective in preventing the transmission of HBV in neonates born to CHB mothers (Hu et al., 2012).

The recipient of hepatitis B vaccine in new-born nurseries is dependent on the hospital policies. The likelihood of receiving hepatitis B vaccine increases in birth institutes that have written policies to screen pregnant women for HBsAg and to offer vaccine against HBV to all new-borns compared to institutes that do not have such written policies (O'Leary et al., 2012).

2.4.2.3 Effectiveness of the vaccine

The effectiveness of active passive immunization was found to be 89.5% in children born to HBeAg positive mothers and 97.9% effective in children born to HBeAg negative mothers (Chen et al., 2012).

A cohort study to assess the long term protection of hepatitis B vaccine in a high endemic region found that 78% of vaccine responders (i.e their anti HBs titre was >10 mIU/mL after primary vaccination at birth) had anti HBs titres below protective levels. However, 81% of those developed a rapid prominent increase in antibody levels after the administration of a Hepatitis B vaccine booster 10 years later. The anamnestic response was found to be dependent on mother's past history of HBV infection, concentration of anti-HBs and time since primary vaccination. Offspring of carrier mothers are 2.43 times more likely to respond to the vaccine compared to offspring of non-carrier mothers (Schonberger et al., 2012). Moreover, children who have anti-HBs titre of >100mIU/mL are 2.8 times more likely to

have an anamnestic response compared to those who have a lower titre level (Chaves et al., 2012).

In adults the efficacy of the hepatitis B vaccine was evaluated in a high risk group of gay men in New York City, USA. The placebo-controlled, randomized, double blinded clinical trial found that 87% of vaccine recipients were responsive to the vaccine and developed anti-HBs after 3 months. The percentage increased to 96% after the administration of a booster injection. The concentration of the surface antigen antibodies (anti-HBs) remained unchanged 18 months later (Szmunn et al., 1980).

2.4.2.4 Intrauterine HBV infection

Intrauterine HBV infection is the transplacental transmission of HBV that cannot be prevented by hepatitis B vaccine. The risk of transplacental transmission increases with the mothers' HBeAg status. HBeAg positive mothers have a 70-90% risk of transmission without administration of prophylaxis. Those born to HBeAg positive mothers have 40.3-fold greater HBsAg rate than those born to HBeAg negative mothers (Chen et al., 2012) (Xu et al., 2002).

The risk also depends on the concentration of HBsAg & HBV DNA titres in the pregnant woman. One study showed that active-passive immunoprophylaxis achieved 100% efficacy in children born to mothers with HBV DNA concentration of <150pg/mL. However, this has been reduced to 68% in children born to mothers HBV DNA concentration of >150pg/mL (del Canho et al., 1997).

Other factors that increase the risk of intrauterine transmission include threatened preterm labour, HBV infection in villous capillary endothelial cells in placenta, transplacental leakage of maternal blood, exposure to cervical secretions and maternal blood during labor and delivery and specific allelic mutations in maternal blood (del Canho et al., 1997) (Tran, 2012).

Treatment of pregnant women remains controversial due to insufficient evidence on its safety and efficacy of preventing transmission. Anti-viral therapy with lamivudine for pregnant women with abnormal ALT levels, positive for HBsAg and HBeAg, have HBV DNA $\geq 1.0 \times 10^7$ copies/mL, during the gestation period between 24-32 weeks, decreases intrauterine HBV infection along with the vaccine and immunoprophylaxis for the new-born babies (Yu et al., 2012).

2.4.3 Hepatitis B screening programs

In spite of having an effective vaccine that reduces the prevalence of the HBV infection in children, time is needed to achieve a sufficient prevalence of immunity so that HBV can no longer spread. Therefore, HBV screening and treatment of high risk groups will add to the control of hepatitis B.

Currently, offered screening programs include: antenatal screening of pregnant women in many countries, screening of ethnic groups (e.g. Maori, Pacific Islanders and Asians over the age of 15 years born before implementation of neonatal vaccine) for CHB and HCC in New Zealand, screening of children and adolescents before entering kindergarten or schools in China, and screening of people applying for a residential visa in Singapore (Mohamed et al., 2004). Additional screening of STD clinic attendees may increase the control of HBV transmission in low endemicity regions (Goldstein et al., 2002) (van Duynhoven et al., 1997).

3 EPIDEMIOLOGY OF HEPATITIS B

This section summarises the global epidemiology of HBV infection, then looking specifically at Oman.

3.1 Search strategy for the literature review

The starting point for this literature was the World Health Organization (WHO) publications on hepatitis B which give brief information regarding the clinical aspects, the epidemiology, the modes of transmission and the burden of the disease. Then, article databases were searched using the following terms; “HBV”, “hepatitis B”, “HepB”, “chronic”, “acute”, “genotype”, “epidemiology”, “incidence”, “prevalence”, “risk factors”, “transmission”, “family”, “IDU”, “blood transfusion”, “dialysis”, “surgery”, “piercing”, “barbers”, “shaving”, “burden”, “HCC”, “hepatocellular carcinoma”, “cirrhosis”, “liver fibrosis”, “outcome”, “HCV”, “alcohol”, “co-infection”, “prevention”, “treatment”, “vaccine”. Further research using more specific key words was conducted throughout the writing process. The data bases searched were Ovid via Medline, PubMed, Scopus and Google Scholar.

There was not much research of interest conducted in the *Gulf Cooperation Council (GCC)* or Arab countries; therefore, studies from the Middle Eastern countries such as Turkey, Iran and Pakistan were included for the purpose of comparison. Full text articles published in English were included.

3.2 Global descriptive epidemiology of hepatitis B

3.2.1 PERSON:

Age

The age at which hepatitis B occurs is dependent on the mode of transmission and determines the outcome of the disease (see 2.3.1). In areas where early horizontal transmission is more frequent, prevalence of HBV infection is lower in new-borns compared to young children. In Africa, for example, HBsAg positivity increases after the age of 6-12 months and the highest seroprevalence is found in children aged 3-5 years (Custer et al., 2004). Similarly, in Saudi Arabia in 1991, HBsAg was highest in children of 1 year of age with a positivity rate of 9.7%, which decreases with age (Al-Faleh et al., 1992).

Where adult horizontal transmission is mostly common, the incidence of HBV infection is found to be higher in young adults. In urban areas of South and Central America for example,

hepatitis B surface antigen is highest in the age group of 20-40 years and lowest in children under the age of 12 years. Findings from Eastern Europe are also consistent where HBsAg incidence is higher in persons aged 20-29. However, a different pattern is found in Western Europe where seroprevalence of HBsAg was found to be three times higher in persons older than 50 years compared to persons aged 25-35 years. This may suggest a decrease in horizontal transmission of HBV over time (Custer et al., 2004). In the United States, the incidence of acute hepatitis B decreased by 89% in the age group 0-19 years between 1990 and 2002 (Centers for Disease and Prevention, 2004). The decline was also noted in the age groups 20-39 and ≥ 40 by percentages of 67% and 39% respectively from 1990 to 1998. However, the incidence in the latter age groups increased after 1998 by 5% in males aged 20-39 years, and 20% and 31% in males and females respectively older ≥ 40 years.

Finally, in Egypt, all three types of transmission modes are evident. When comparing the North and South of Egypt, HBsAg seroprevalance is highest in teenagers aged 4-18 years and in adults aged 39-48 respectively (Custer et al., 2004).

Gender

Globally, HBsAg carriage is generally found to be higher in males than in females. When comparing the general population in Thailand, HBsAg is 1.7 times as high in males than in females, and three times as high among male blood donors compared to female blood donors (Custer et al., 2004). In Kuwait, the incidence of AHB is two times higher in males than in females (Toukan and Group, 1990). In the USA, the ratio of male to female HBsAg incidence was found to be 1.5 in 1990 and 1.7 in 2002 (Centers for Disease and Prevention, 2004). Moreover, there has been an overall decrease in HBV carriage rate which is noted more in females than males. This observation was also noted in countries in Africa, Western Pacific and Asia (World Health Organization, 2002). It is suggested that females are more likely to clear the HBV and develop antibodies against it (Al-Faleh et al., 1992). On the contrary, when studying Saudi children, no significant difference in HBsAg prevalence was noted between genders (Al-Faleh et al., 1992).

Ethnicity

Epidemiological studies have reported different distribution in the prevalence of hepatitis B by ethnic grouping. For example, this is noted in North America where higher prevalence of HBV infection in Native Alaskan, Ethnic and Native Canadian populations is reported.

Similarly, in areas of South and Central America, seroprevalence is higher in native populations (Custer et al., 2004). In New Zealand, the prevalence of chronic hepatitis B, by the year of 2002, was found to be 7.3% in Pacific Islanders, 6.2% in Asians, 5.6% in Maori and 2.8% in other ethnicities (Robinson et al., 2005).

3.2.2 PLACE:

HBsAg carriage prevalence shows geographical variations and ranges between 0.1 to 20% globally (Custer et al., 2004). WHO divides the world into three zones according to the prevalence of HBsAg carriage. The three zones are: low endemicity where the prevalence of carriage is <2% which includes North, West and Central Europe, North America, Australia and New Zealand; intermediate endemicity where carriage is 2-7% such as in Eastern Europe, Mediterranean, Russia and the Russian Federation, South-west Asia and Central and South America; and the high endemicity zone with a carriage of 7-15% such as parts of China, South East Asia, and Tropical Africa (World Health Organization, 2002)

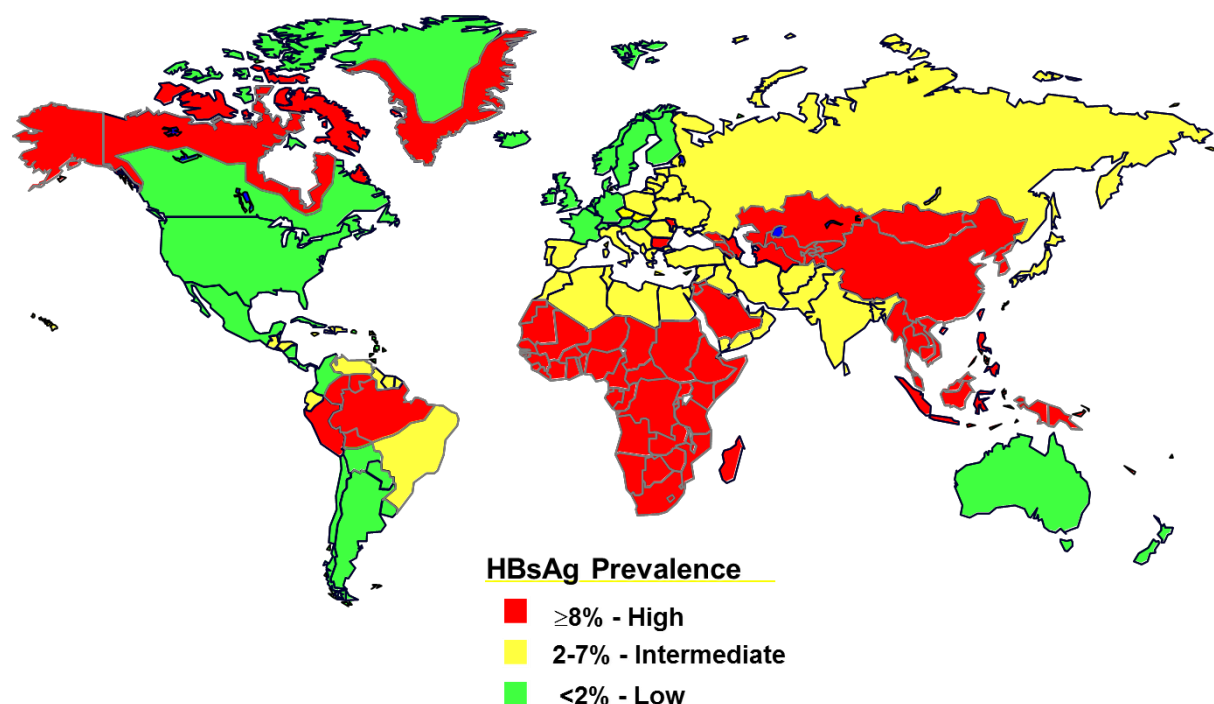


Figure 3.1 Geographical distribution of chronic hepatitis B.

Reference: (World Health Organization, 2002)

The Western Pacific region (except New Zealand, Australia and Japan) has the highest number of hepatitis B carriers with around 150 million chronically infected individuals (Lesmana et al., 2006). Africa is the second highest region with 58 million chronically infected individuals (Custer et al., 2004)

Geographical differences in hepatitis B prevalence within a country are also noted. In Egypt for example, the prevalence of HBsAg was higher in Upper Egypt 11.7% than in Lower Egypt (8%), with 88% of these populations found to be positive for anti-HBc (Sherif et al., 1985). This was also noted in Iran where positivity for HBsAg and anti-HBc was higher in rural areas compared to urban areas (OR 3.0, 95% CI 1.2-7.2, $p=0.01$) (Merat et al., 2009).

3.2.3 TIME:

There has been a worldwide reduction in hepatitis B after the development of a vaccine in 1982 (Lavanchy, 2004). Taiwan, for instance, was one of the first countries to initiate universal immunization against HBV in July 1984. Since then, the chronic HBV carrier rate has decreased from 10%-20% to 1%-2% (Chen et al., 2012). There also has been a reduction in the incidence of HCC by around 67% and the incidence of infantile fulminant hepatitis in Taiwan.

Similar results were noted in Africa. HBsAg prevalence was significantly reduced in children in Gambia and Senegal from 10% to 6% and from 18.7%-2.2% respectively (Custer et al., 2004). In addition, the age group of 15-24 in 1988 was compared to the same age group 6 years later in Italy noting a reduction in AHB by half.

In the United States, the incidence of AHB decreased by 67% over the time period of 1990-2002 (Centers for Disease and Prevention, 2004), and by 88% over the time period of 1991-2008 (Mitchell et al., 2011). However, the incidence has increased in immigrants to the USA.

3.3 Modes of transmission and risk factors

There are two major modes by which HBV is transmitted. These are vertical and horizontal transmission. Transmission of HBV varies depending on the prevalence of HBsAg in each country. In hyper-endemic areas such as Southeast Asia and Western Pacific, perinatal transmission seems to be the major mode of HBV transmission. Intermediate endemicity of hepatitis B in areas such as the Middle East is attributed to early horizontal transmission of the virus in children of preschool age (Toukan and Group, 1990, Toukan, 1990). Horizontal transmission of hepatitis B in adults has been shown to be the main mode of transmission in low endemicity areas such as North America and Europe (Custer et al., 2004). The mode by which HBV is transmitted is a key aspect in determining the prognosis of the infection. The risk of developing CHB increases in patients who acquire the virus vertically or in early childhood (<5years).

HBV is 100 times more infectious than HIV and can survive outside the human body for at least seven days. HBsAg has been found in most bodily secretions of infected individuals. These include blood, vaginal and menstrual fluids, semen, saliva, perspiration, breast milk and tears, each with a different infectivity risk (Lavanchy, 2004) (World Health Organization, 2002). The risk of transmitting the virus is mainly dependent on the amount of the virus DNA in the serum, which is found higher in HBeAg positive patients (Shiffman, 2010).

3.3.1 Vertical transmission

Perinatal transmission of HBV is the predominant mode of transmission in high endemicity regions such as Asia and Africa. This mode is responsible for most of the chronic cases and hence increasing the risk of developing cirrhosis and HCC (more details in 2.4.2.4).

In the Middle East, perinatal transmission of HBV is thought to play a secondary role in the endemicity of hepatitis B. When assessing the effect of mother to child transmission of HBV in Arab countries, HBsAg positivity appeared in 21% of infants born to HBsAg positive mothers (Toukan and Group, 1990) (Toukan, 1996). The majority of transmission occurred in mothers positive for HBeAg compared to mothers negative for HBeAg (94% vs. 10% respectively). The prevalence of HBeAg positivity was found to be 13% in HBsAg positive mothers.

3.3.2 Horizontal transmission

3.3.2.1 Household contact and spousal transmission

Household contact with HBV infected members is a common way of spreading HBV infection in areas with HBsAg endemicity of 2-7% such as the Middle East. It is affected by the characteristics of the household such as family size, number of infected individuals, their relationship, socio-economic status of the family and members' serologic status.

One study conducted by Toukan et al. in Jordan in 1990, found a 49% increase in HBsAg positivity rate in families consisting of more than six members when compared to families of 2-5 members ($p < 0.01$) (Toukan, 1990). A more recent study by Bawazir et al. showed supporting results where household size of 5-9 members are 2.9 more likely at risk of hepatitis B infection compared to smaller family size (AOR= 2.9, CI= 1.1-7.6) (Bawazir et al., 2011). Similarly, a study from Turkey showed a significant increase in the rate of HBV transmission in families with ≥ 5 members ($p < 0.05$) (Urganci et al., 2013). Transmission can be explained by shared use of intimate objects such as utensils, tooth brushes, bottles, toys, razors and other objects (Bawazir et al., 2011).

Toukan et al. also reported that the prevalence of HBV infection rose from 57% to 98% in families when the number HBV carriers increased from 1 to 3 respectively ($p < 0.05$) regardless of the size of the family (Toukan, 1990).

One other feature that affects the transmission of HBV in a household is the relationship between the individuals. The prevalence of HBV carriage in children of an HBsAg positive mother was greater than those of HBsAg negative mothers; however, the HBsAg positivity of the father did not significantly increase the carriage rate in the children as that of the mother (Toukan, 1990). The reason why vertical transmission was not considered to be the mode of transmission was due to the low HBeAg positivity status in HBsAg mothers and women of child bearing age. Moreover, the authors found no child under the age of one to be positive for HBsAg, hence attributing the transmission to close mother to child contact compared to that with the father. Similarly, it was found that persons who live with an HBsAg positive parent are 3.25 more likely to get infected with HBV than those who live with HBsAg negative parents (95% CI: 1.73-6.12, $p < 0.05$) (Ozer et al., 2011).

Most of the contact reported above is described as intimate non-sexual contact. When trying to assess the role of spousal transmission of HBV, a case control study by Ozer Ali in Turkey

found that having an HBsAg positive spouse increases the risk of being infected by the virus by 4.3 times (95% CI: 2.12-8.53, $P < 0.05$) with the risk being found higher in female patients compared to males, especially in patients < 30 years. They also found that 61.2% of the women were likely to have acquired the virus from their positive partner (excluding sexually inactive and haemodialysis patients) (Ozer et al., 2011)

3.3.2.2 Sexual activity

Sexual activity is a major risk factor for acquiring AHB, mainly in Western societies where the prevalence of HBV is low (Custer et al., 2004). In the United States, heterosexual relationships with one infected partner or multiple partners accounts for 27.4% of acute hepatitis B infections, and homosexual relationships account for 13.5% of infections (Goldstein et al., 2002). Moreover, a study to measure the prevalence and risk factors for HBV infection among STD clinic visitors in the Netherlands found that HBV prevalence in STD clinic visitors is higher than the general population. They also found that the risk factors for current infection of HBV (HBsAg positive) were a history of STD and number of partners in the past half a year (inversely). The inverse association between HBsAg positivity and the number of partners in the past six months is contradictory to other studies. This is suggested to result from confounding by non-investigation regarding perinatal transmission mode as well as the inappropriate time frame to assess exposure to the virus. On the other hand, the risk factors for previous infection (HBcAg positive) were found to be commercial sex, number of lifetime partners, homosexual contact, orogenital contact (inverse) and history of STD. (van Duynhoven et al., 1997)

3.3.2.3 IDU

IDU is one of the most commonly identified risk factors for hepatitis B besides sexual activity in the regions of North America and Europe (Custer et al., 2004). It has been reported that 18.2% of AHB in the USA is attributed to IDU (Goldstein et al., 2002). The incidence of AHB in this high risk group has decreased by 90.6% over the period from 1988-1998, but this was accompanied with an increase in the age of IDU associated HBV transmission.

The prevalence of HBV infections among injecting drug users in the Middle East varied considerably between countries. In Pakistan, a HBV prevalence of 6% was found in IDU risk group in the city of Quetta (Ali et al., 2009), while the prevalence of HBV among IDU in Ahvaz, Iran was as high as 44.3 % (Jahangirnezhad et al., 2011).

In Saudi Arabia HBV DNA was found to be positive in 12% of IDU, being ten fold higher than in the general population (1.7%) (Alzahrani et al., 2009).

3.3.2.4 Health-care associated infections

3.3.2.4.1 Unsafe injections

Unsafe injections in health care settings are one of the ways HBV is transmitted in developing countries. It was suggested that 58% of HBV infection in the Eastern Mediterranean region is attributed to unsafe injections each year (World Health Organization, 2009). This results from the reuse of infected, unsterilized needles in the health care settings.

WHO estimates that the average person in Southeast Asia receives four injections annually, with the majority being unnecessary and three quarters unsafe or reused (Ali et al., 2009). In Pakistan, the attributable risk for therapeutic injections was found to be 53% in patients with AHB. The reason for the increased risk of HBV transmission via unsafe injections results from patients' preference of injectable to oral medications, unawareness of some health care workers about the risk of transmitting blood borne pathogens via unsterile needles and financial limitations of some medical institutes. Another example is Moldova where injections in the healthcare setting are major source of HBV transmission as a result of the widespread reuse of inadequately sterilized single-use syringes (Ozer et al., 2011).

3.3.2.4.2 Receipt of blood and blood products

Blood transfusion is one of the most efficient modes of HBV transmission. Studies in Egypt found an association between blood transfusion and hepatitis B among patients with chronic haematological disorders in need of regular blood transfusion (Gasim et al., 2013). Similarly, in the time period of 1997 to 2009 in the USA, HBV was found to be 5.4% higher in patients with sickle cell disease (Nouraie et al., 2012). Patients with sickle cell disease were found to be 1.82 times more likely to have concurrent infection with HBV than patients without sickle cell disease (95% CI 1.24-2.68).

3.3.2.4.3 Organ transplantations

Organ transplantation is one of the routes in which HBV can be transmitted from an infected individual to a naïve recipient. The virus can be introduced to the body percutaneously by either infected organs or blood products (Kennedy et al., 2005).

The risk of viral infection increases among those undergoing commercial transplants, especially if it was conducted in a high endemicity region. For example, when comparing

Saudi patients who have undergone renal transplant in India to locally transplanted patients from the period of 1978-1993, it was found that the risk of acquiring hepatitis B viral infection was 6.7% higher when conducted abroad (8.1% vs. 1.4%) (Kennedy et al., 2005).

3.3.2.4.4 Haemodialysis and other medical procedures

Haemodialysis has been identified as a risk factor for the transmission of HBV. In Turkey, patients undergoing haemodialysis were found to be 8.32 times more at risk of HBV infection, especially in patients over the age of 31 ($p < 0.001$) (Ozer et al., 2011).

In Brazil, the prevalence of HBV infection was higher among haemodialysis patients compared to the general population (Neto et al., 1995). Treatment with haemodialysis (excluding transfusion of blood) significantly increased the risk of viral transmission. This indicates environmental transmission of the virus which was supported by a decrease in incidence with isolation of patients tested positive for the virus.

In Asia-Pacific countries the incidence of HBV infection in haemodialysis reflects the endemicity of the virus in that country. For example, in Japan where HBV endemicity is low, the incidence of HBV infection among haemodialysis patients was 1.3% compared to 14.6% in China which is a high endemic country (Johnson et al., 2009).

Other medical procedures such as surgeries, endoscopy and dental interventions were identified as a risk factor for transmitting HBV. In a case control study in Iran, for example, history of major surgery and endoscopy was positive in 44% and 55% of participants respectively and were found to be independent risk factors for CHB infection (Jahangirnezhad, 2011). However, several studies from Arab and African countries failed to show any significant impact of surgical procedures, home deliveries and dental procedures (Gasim et al., 2013).

3.3.2.5 Occupational risks

An association has been established between HBV transmissions and some professions depending on the exposure to infected individuals. Examples of these professions include doctors, nurses, dentists, barbers, police men and sex workers.

In Pakistan, health care workers were found to have a higher prevalence of HBV infection compared to the general population (6% weighted average) which is mainly caused by the lack of universal vaccination of high risk groups (Ali et al., 2009). A cross sectional study in

Iran in 2011 found that 5% of positive HBV carriers were nurses (Jahangirnezhad et al., 2011).

On the contrary, some studies found either low or no evidence of hepatitis B infection among HCW. This can be explained by their highest compliance rate with HBV vaccination program due to their exposure to recurrent informational activities about the disease (Ozer et al., 2011).

3.3.2.6 Others

Other risk factors that are thought to contribute to the transmission of HBV include shaving with a barber, tattooing, piercing and acupuncture. These practices are expected to introduce the virus percutaneously to the body; however, the significance of these practices in spreading the disease has been minimally investigated.

Studies from the Middle East showed barbers had low to moderate awareness that hepatitis can be transmitted by contaminated razors, 46% of shaves were done with reused razors, HBV DNA was detected in 6.6% of used razor blades and cuts from barbershops are associated with HBV transmission with an odds ratio of 4.74 (Ali et al., 2009) (Al-Rabeei et al., 2012) (Eroglu et al., 2010) (Alswaidi and O'Brien, 2010).

As for tattooing, in a cross sectional study in Iran, tattooing was found to be an independent risk factor for being chronically infected with HBV (Jahangirnezhad et al., 2011).

3.4 Epidemiology of hepatitis B in Oman

Oman is categorised as a country with intermediate endemicity for hepatitis B with a prevalence of 2-7% of the total population being infected with the virus. Following the geographical distribution of HBV genotypes, genotype D is expected to be the most prevalent genotype in Oman (Kramvis et al., 2005). In this section, a summary of what is known about hepatitis B in Oman is outlined.

3.4.1 Disease surveillance system in Oman

A *Disease Surveillance System* has been functioning in Oman since 1991. This system aims to reduce the incidence of health care associated infections, to set up an effective epidemic preparedness system, to achieve the highest possible levels for early detection of communicable diseases, and to reduce the incidence of vaccine-preventable and non-vaccine-preventable communicable diseases. Specified infectious diseases are required to be notified to the system and are classified in three groups depending on the time frame in which they have to be notified within. Hepatitis B is classified in Group B diseases which must be notified within seven days of presentation. Patients presenting with symptoms of acute hepatitis (jaundice, malaise, anorexia with supporting laboratory findings i.e. elevated bilirubin or ALT) are to be screened for viral hepatitis (Bhat et al., 2005). The blood sample is firstly screened for hepatitis A virus. Negative cases will then be screened for HBsAg, and if positive, will then be tested for HDV to rule out dual infection. However, if HBsAg status is negative, the blood sample will be tested for HCV. Cases negative for HCV will then be screened for hepatitis E virus.

3.4.2 Descriptive epidemiology of the incidence of acute hepatitis B in Oman

The MoH in Oman reports the number of notified cases in their *Annual Health Reports*. Data derived from these reports are presented in graphs here in order to describe the incidence of AHB by time, person and place. This will be compared with the situation in Saudi Arabia where published literature was available.

Figure 3.2 shows the incidence of acute hepatitis total (includes HAV, HBV, HCV, HEV, HDV and others) in comparison with AHB. It can be seen that the pattern of AHB in Oman was consistent from 1991 to 1996. In 1999, the incidence of HBV was a very small proportion of total acute hepatitis. The overall decreases in acute HBV cases were mainly attributed to the introduction of HBV vaccine in 1990 to the *Expanded Program of Immunization*. However, the steep decline noted in 1997 was due to the changes in the

confirmatory laboratory testing from latex test to ELISA test which is more specific (CDSC Oman, 2005). Other explanations of the decline is the vaccination of high risk groups, improvement of lifestyle, universal screening of blood and blood products in blood banks, and increased knowledge and safety in clinical practices (Abdo et al., 2012a).

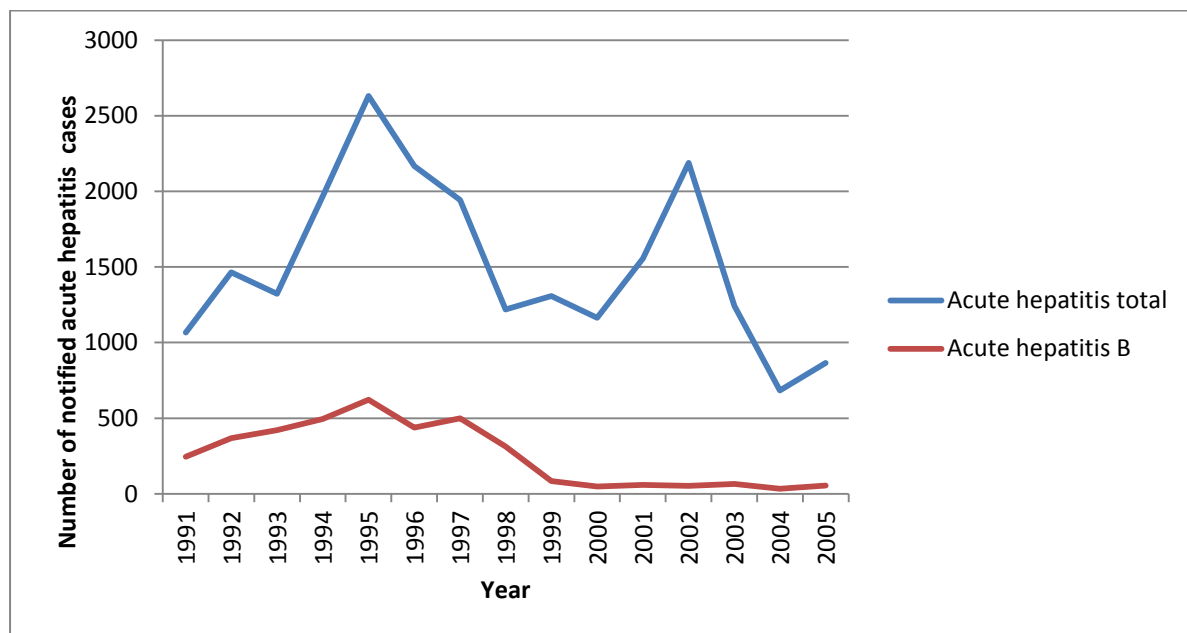


Figure 3.2 The incidence of acute hepatitis total and hepatitis B in Oman since 1991 till 2005

Data source: CDSC quarterly reports

Figure 3.3 shows the number of notified cases of AHB from 1995 to 2012 in Oman by age. It can be seen that the age groups of 1-4 years and 5-9 years accounted for most of HBV cases before the year 2000. This is compatible with early horizontal transmission of HBV in young children being the most predominant mode of HBV transmission in the Middle East (Toukan, 1990). Symptomatic hepatitis B is rare at this young age (Shiffman, 2010) and only acute (mainly icteric) cases are screened for the virus surface antigen (HBsAg). Also, jaundice is also a symptom of haemolytic blood disorders such as haemoglobinopathies, which are prevalent in Omani children (Al-Riyami and Ebrahim, 2003) and which may explain the high detection rate at this young age. Symptomatic haemoglobinopathies was found to be 3.1 per 1000 live births during 1989-1992 (Rajab et al., 2000).

A decline in the incidence of hepatitis B in these two age groups started in 1997. After 2004, no HBV positivity was reported in these age groups and adults accounted for most of the cases. A study from Al Dakhliya region found a significant linear association between HBV

positivity and increasing age ($p<0.001$) with a mean age of 32.4 ± 16.2 years (Bhat et al., 2005). In Saudi Arabia, a higher mean age of HBV infection of 37 ± 16.2 years was reported from 2000 to 2007 (Memish et al., 2010). The majority (97.9%) of them were above the age of 15 ($p<0.001$).

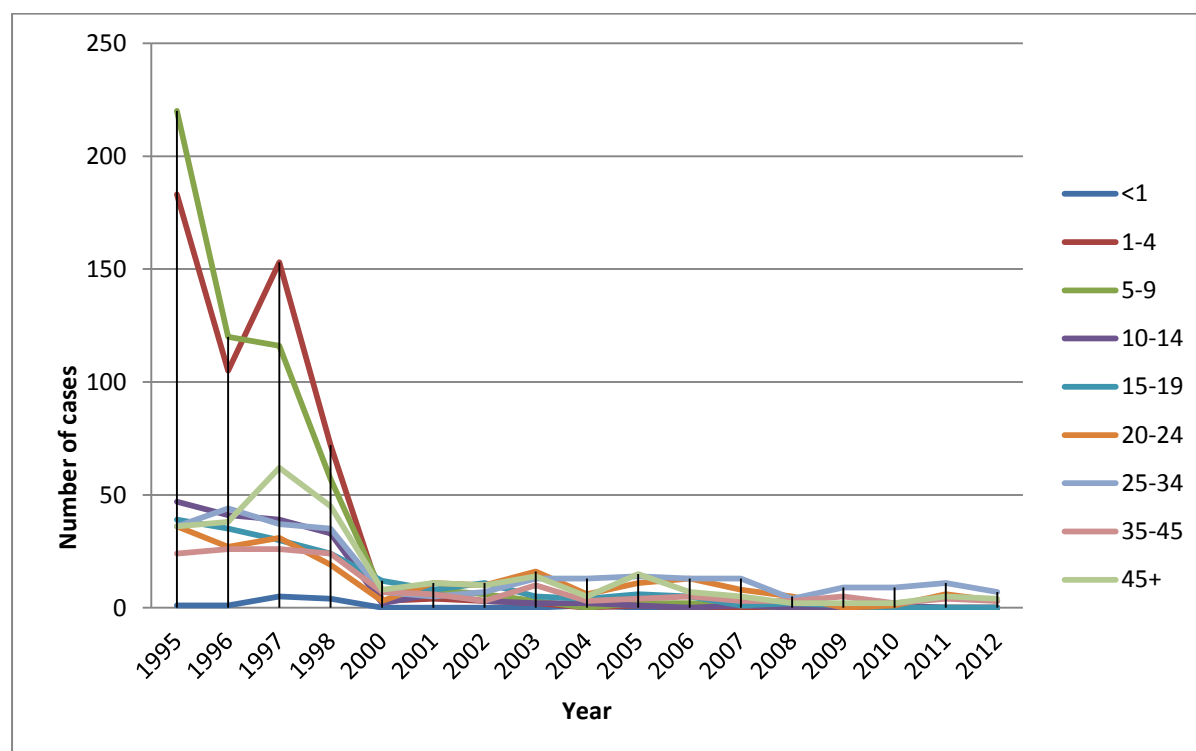


Figure 3.3 The number of acute hepatitis B from 1995 to 2012 by age

Data source: CDSC quarterly reports

Unfortunately, data regarding the incidence of hepatitis B by gender is not reported by the *Communicable Diseases Control and Surveillance Department* in Oman. However, a study from Al Dakhliya region found no significant association between HBV infection and gender from 2003 to 2004 (Bhat et al., 2005). Similar male to female proportion was also noted in another study that looked at the characteristics of hepatitis B in a sample of patients followed up at a tertiary referral centre in Muscat (Al-Naamani et al., 2013). On the contrary, male predominance for HBV positivity in Saudi Arabia was significant ($p<0.001$) with a relative risk of 1.8 in adults (Abdo et al., 2012a).

Figure 3.4 shows the cumulative incidence of hepatitis B (per 100,000) in the regions of Oman from 2003-2010. It is shown that Al Wusta and Musandam are responsible for most of HBV cases per 100,000 people. This is possibly because these regions are more rural than the other regions. The contrary is seen in Muscat, which is the most developed area in Oman.

Residence in a rural area was found to be a risk factor for HBV infection in Iran (Merat et al., 2009).

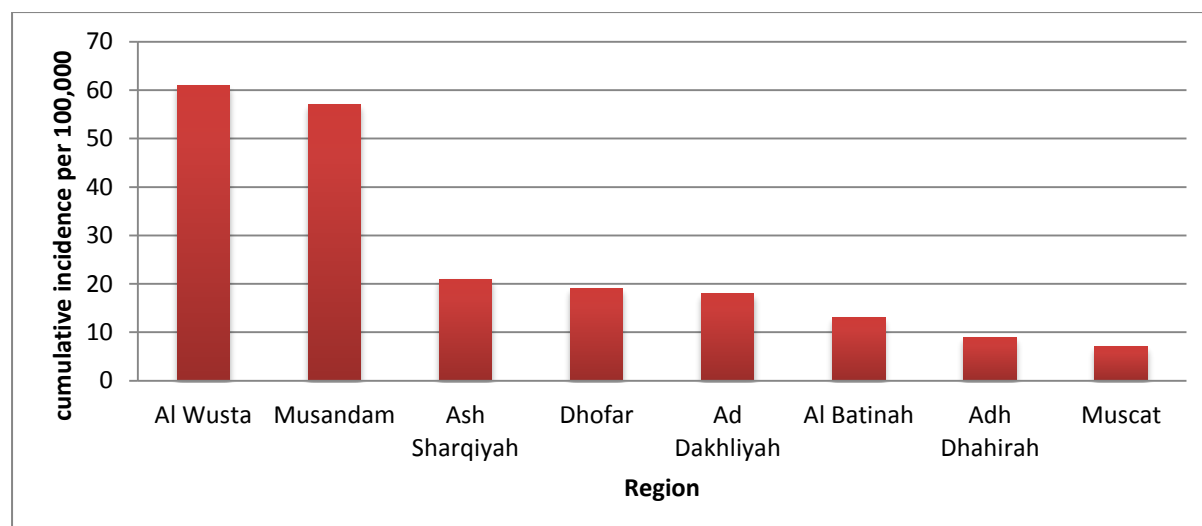


Figure 3.4 The cumulative incidence of hepatitis B (per 100,000) in Oman from 2003-2010 by regions.

Data source; CDSC and 2010 census data

The data above underestimates the real incidence of acute hepatitis B in Oman. This is because symptomatic hepatitis is directly dependent on the age of infection, as discussed in chapter two (see 2.3.1). Jaundice develops in only 30% of acutely infected patients which means that the real incidence of AHB is underestimated by at least 70% by this passive surveillance. Moreover, differentiating between AHB and CHB with acute flare is not possible by screening for HBsAg alone. Anti-HBc IgM is the most specific marker for acute infection. However, it is not available for screening due to its high cost (Bhat et al., 2005).

3.4.3 The prevalence of hepatitis B in specific Omani populations

There has not been any population-based study conducted to calculate the prevalence of hepatitis B in Oman. However, studies investigating the prevalence of the infection in specific populations such as pregnant women and blood donors are available.

Al Awaidy et al conducted a cross sectional study in 2005 to evaluate the prevalence of hepatitis B markers among pregnant women in Oman and two other GCC countries; United Arab Emirates and Qatar. The study revealed that HBsAg positivity was higher among Omani pregnant women (7.1%) compared to those in other GCC states (UAE 1.5% and Qatar 1%) (Al Awaidy et al., 2006). A low proportion of pregnant Omani women were found to be

positive for HBeAg (0.5%). The study revealed that HBsAg positivity was significantly higher in women ≤ 24 years (adjusted OR 2.4, 95% CI 1.367-4.336, $p = 0.0025$). These findings indicate that the risk of vertical transmission of hepatitis B in Oman is not fully eradicated yet. Although HBV vaccine was introduced at the same time in these three countries, the prevalence remains higher in Oman which raises questions regarding the efficacy and coverage of the vaccine in Oman.

Furthermore, Kaminski et al. evaluated the prevalence of HBV markers among Omani blood donors in the same year (Kaminski et al., 2006). They found that 20.5% of blood donors had been infected with HBV in the past (anti-HBc positive). They also found that HBsAg positivity was present in almost 3% of blood donors. The findings of these two studies by Al Swaidy and Kaminski are compatible with the estimated intermediate national prevalence of hepatitis B in Oman.

3.4.4 Risk factors associated with hepatitis B in Oman

No studies in Oman were specifically aimed to evaluate the risk factors associated with HBV transmission among Omani patients. However, some studies revealed an association between some medical practices and HBV positivity. When studying transplantation patients, 2.3% of patients from Oman and UAE developed a positive status of HBV infection after undergoing a commercial renal transplant in Bombay, India, from 1984-1988 (Salahudeen et al., 1990). Moreover, the prevalence of HBsAg is significantly higher in haemodialysis and renal transplant patients than in nephrology clinic patients ($p = 0.05$) (Aldhahry et al., 1994). These risks are expected to minimally contribute to HBV transmission at the present time due to advances in medical safety policies. When studying patients already infected with HBV, Al Naamani et al. reported positive family history of hepatitis B, traditional cautery (*wasm*), body piercing(s), surgery(ies) and blood transfusion(s) in 70%, 65%, 40%, 18.2% and 4.5% of patients respectively (Al-Naamani et al., 2013).

3.4.5 Control and prevention of hepatitis B in Oman

The hepatitis B vaccine was introduced to the *Expanded Program of Immunization* in August 1990 aiming to reduce the prevalence of HBV carriage to 2% in the general population. All new-borns well enough to be discharged from the hospital (including pre-mature and low weight infants), are indicated for the first HBV vaccine dose within the first 12 hours of life (Sultanate of Oman Ministry of Health). Active immunization using the three-dose vaccine plus passive immunization by administering hepatitis B immunoglobulins to neonates born to

HBsAg mother regardless of her HBeAg status is followed in SQUH and AFH but not in MoH hospitals. To increase the coverage rate of the HBV vaccination strategy, hepatitis B catch-up school campaigns from 2001-2004 were conducted to vaccinate school children who were born before August 1990.

Other strategies were also implemented by the MoH to improve the control of the diseases in Oman (Sultanate of Oman Ministry of Health, 1994). These include the screening of all family contacts of HBsAg positive patient and vaccinating HBsAg negative children below the age of ten years. Moreover, there is also screening of all blood and blood products for HBsAg which is considered to be the gold standard screening marker for blood donors, with improvement in its sensitivity since it was first introduced in early 1970s (Roth, 2007). However, HbsAg may be undetectable in some chronic carriers with reduced levels of HBsAg, patients in the AHB window period and mutations in the 'a domain'. Therefore, some countries introduced testing for anti-HBc alongside HBsAg testing to further reduce the risk of transmissible infection. In Oman, evidence of occult HBV infection was noted in 20.5% of HBsAg negative donors (Kaminski et al., 2006) and anti-HBc testing was only introduced in November 2008. Also, the Moh strictly recommends the implementation of precautionary measures while handling blood or body fluids. All health care workers must be immunised against the virus.

Screening of patients in dialysis units for HBsAg is also recommended by the MoH (Executive Board of the Health Ministers' Council for GCC States, 2009). All HBsA negative patients and staff working in the unit are to be vaccinated against the virus. Patients with poor response to the vaccine (anti-HBs<10 mIU/ml) should be revaccinated and retested annually. With respect to HBsAg positive patients, isolation of dialysis machines, areas and staff of infected patients, and disinfection and sterilization of all non-disposable instruments is recommended.

4 MAJOR RISK FACTORS FOR ACQUIRING HEPATITIS B INFECTION AMONG HBsAg POSITIVE PATIENTS IN OMAN

4.1 Introduction:

Risk factors for the spread of HBV vary between nations depending on the endemicity of the disease. Risk factors specific to the Omani population have been minimally evaluated. Family history of hepatitis B, *wasm* (an alternative medical practice used to treat jaundice by applying a hot metal implement to the skin), body piercings and surgeries were found common among a group of Omani patients (Al-Naamani et al., 2013). Identifying the risk factors associated with the transmission of HBV in Oman is essential to achieve effective control of the infection and to explore the groups that are at higher risk. It would also enable us to detect any changes/shift in the mode of the transmission.

This chapter will describe the methods, results and discussion of a cross sectional study which aims to identify the prevalence of HBV transmission risk factors among Omani patients with active hepatitis B.

4.2 Aims:

- Identify the prevalence of risk factors for acquiring HBV in Omani HBsAg positive patients.

4.3 Methods:

Recruiting participants:

Subjects were recruited from outpatient clinics. At SQUH, the hepatitis outpatient clinic is run weekly. Along with other hepatitis aetiologies, HBV positive patients are seen routinely at this clinic for consultations. During the period from 27 February 2013 till 4 July 2013, a total of 17 clinics were attended and the clinic was closed for two weeks. The medical files of patients waiting at the clinic were checked for HBsAg positivity. Those positive for HBsAg were approached by me and asked if they would be interested in participating in a study. Patients agreeing to participate were then taken to a private room where the study was explained in more detail to the participants. An information sheet was given to them to read before signing the consent form. For participants who could not read, the information sheet was read and explained to them by either me or their chaperone. Not all HBsAg positive

patients were approached to participate, as some did not attend scheduled appointments or I was unable to see them.

At AFH, patients were recruited by two different methods. The first method was face to face interviewing of patients attending Dr Al Naamani's, hepatology consultant at AFH, OP clinic every week. Not all HBV patients followed at AFH were seen by Dr Al Naamani, but clinics were run on different days and I was only able to attend that one clinic. From 11 March 2013 till 2 July 2013, a total of 13 clinics were attended (11 with Dr Al Naamani and 2 with Dr Kamath). Unlike at SQUH, patients were referred to be seen by me by the doctors either before or after their consultation.

The other method of recruiting patients from AFH was by telephone interview. The data and contact details of 156 hepatitis B patients were given to me. Those patients had taken part in a recent retrospective study that looked at the characteristics of HBV infection. The data included patients' demographic characteristics, history of HBV risk factors, and laboratory findings. Only the demographic data and history of HBV risk factors were used. Patients were called to inquire about other risk factors that were not included in the previous study such as hepatitis B awareness and history of endoscopy, dental treatment, traditional phlebotomy, barber shaving and circumcision. As this study was conducted from 2009 till 2011, patients' date of birth was obtained to calculate their current age. The study was explained to the patients and verbal consent was obtained before starting the interview.

Ethical approvals were obtained from University of Otago, SQUH and AFH Human Ethics Committee prior to commencing the study.

Inclusion criteria:

Omani patients with positive HBsAg aged 13 years and above were attending the hepatology outpatient clinics during the time frame mentioned above. Patients who agreed to participate and sign the consent form, or gave verbal consent were included in this study. As for patients interviewed over the phone, those with available contact numbers were included.

Exclusion criteria:

HBsAg negative HBV patients, non-Omani patients, patients seen twice and those with incomplete questionnaires were excluded from the study.

The questionnaire:

Data was collected using a two page questionnaire recording patients' demographic characteristics such as age, gender, marital status, educational level and occupation (Appendix). Participants were also questioned about their immunization history and their frequency of exposure to identified and potential risk factors for HBV transmission prior to their date of diagnosis. Those risk factors include: history of hospitalization, major surgeries, organ transplantation, blood transfusion, endoscopy, hemodialysis, chemotherapy, dental visits and contact with infected people.

The questionnaire was derived from known and suggested risk factors in the international literature and the questions were also discussed with the senior hepatology consultants at AFH and SQUH. Each interview took five to 15 minutes and patients were given the chance to ask any questions before and after finishing the questionnaire.

All questionnaires were administered by the interviewer, which was always me, during the interview, except for one patient who requested the Arabic version of the questionnaire and filled it in by himself.

4.4 Analytical methods:

Demographic variables

Participants were grouped in three different age groups depending on the HBV immunization program in Oman. The three age groups were; 13-<23 for patients born after the introduction of HBV vaccine to Expanded Program of Immunization in August 1990, 23-28 for patients born before August 1990 but who presumably had completed the catch-up school vaccine campaigns completed in 2004-2005, and finally >28 for patients born before that.

Depending on marital status, patients were classified as "ever married", which also include divorced and widowed, and "non-married", which included single and engaged participants.

Occupations were classified as non-risk occupations and high-risk occupations. High-risk occupations included nurses, medical doctors, medical orderlies, medical assistants, medical students, policemen, dentists, sex workers, blue-collar employees, barbers and beauticians (Jahangirnezhad et al., 2011) (Ali et al., 2009) (Alavian et al., 2007).

Grouping of risk factors

Risk factors for the transmission of HBV were grouped as nosocomial, family exposure or high risk behaviors. Nosocomial risk factors included history of hospitalization, major surgery, organ transplantation, endoscopy, blood transfusion dialysis and dental treatment. Family related risk factors included; family history of HBV, current living with HBV infected individuals (later classified as sexual or non-sexual contact), mothers' history of HBV and finally, family history of liver disease. High-risk behaviours included: unawareness about HBV infection, piercings, regular shaving with a barber, wasam, traditional phlebotomy, acupuncture, circumcision, multiple sexual partners. Participants were asked for the place where piercing or circumcision was done, which was then classified as clinical and non-clinical settings.

During the interviews, frequency of risk factors was recorded as 0, 1, ≥ 2 . However, this was changed to yes or no for analytical purposes.

Statistical analysis

The sample size required was determined by the number of patients that could be interviewed during the data collection period. This was expected to be 300 patients. In a previous study of CHB carriers in Iran that looked at 560 patients they found that endoscopy, major surgery and tattooing were independent risk factors for CHB with percentages of 54.8%, 44.5% and 8.5% respectively (Jahangirnezhad, 2011). If the situation was assumed to be similar in Oman, a sample size of 300 participants would enable us to estimate the proportion tattooed with 95% confidence intervals of approximately $\pm 5\%$, and the proportion with endoscopy or surgery with 95% CI of approximately $\pm 6\%$.

Epi info version 7 was used to calculate the frequency of HBV transmission risk factors in the total studied population. The risk factor frequency was stratified by age groups (13- <23, 23-28, ≥ 28), sex (male and female) and educational level (pre-secondary, secondary and post-secondary).

A chi-square test was performed to examine the association between risk factor frequency and gender, age or educational level and reported when significant. A P value of < 0.05 was considered significant.

4.5 Results:

Out of 365 HBV positive patients eligible to participate in this study, only 274 were included in the final analysis. A total of 92 patients were excluded (figure 4.1). The number of patients who did not attend the outpatient clinic or who I was unable to interview was not recorded but I estimate it to be one to two patients per clinic (total 30-60 patients).

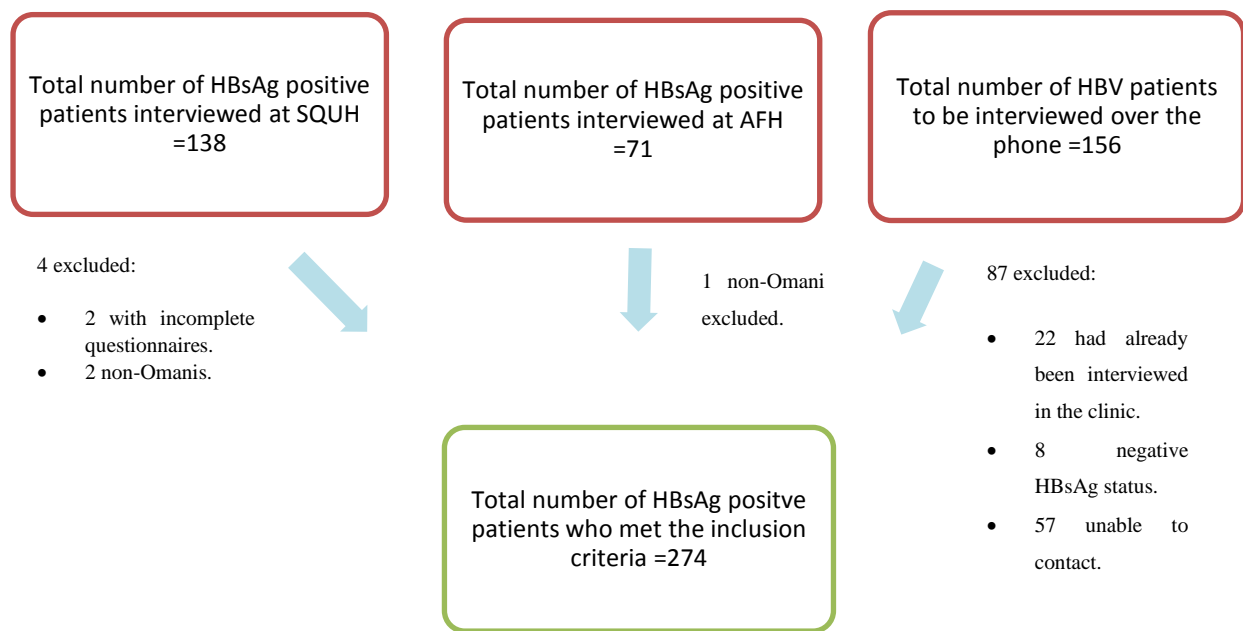


Figure 4.1 Flow chart showing the process of recruiting patients

The demographic features are summarised in Table 4.1. The median age for men was 35.9 year and for women 35.1 year with 75.5% of them in the age range of 20 - 39 (Figure 4.2). The majority of the participants came from Al-Batinah (32.1%), Al-Dakhiliya (25.1%), Muscat (19.0%) and Al-Sharqiyah (16.4%) regions (table 4.1). A minority of participants (3.7%) worked in high risk jobs which included; 3 nurses, 2 policemen, 1 doctor, 1 medical student, 1 medical assistant and 1 medical orderly.

Table 4.1 Demographic characteristics of the participants

Variable	Number	Percentage
No. of participants	274	
Age (years; median (range))	35.5 (19-86)	
Gender		
Male	143	(52.2%)
female	131	(47.8%)
Region		
Al-Batinah	88	(32.1%)
Al-Dakhiliya	71	(25.1%)
Muscat	52	(19.0%)
Al-Sharqiya	45	(16.4%)
Al-Dhahirah	14	(5.1%)
Al-Buraimi	1	(0.4%)
Al-Wusta	1	(0.4%)
Dhofar	2	(0.7%)
Educational level		
Illiterate	15	(5.5%)
Write and read	5	(1.8%)
Elementary	20	(7.3%)
Primary	21	(7.7%)
Secondary	112	(40.9%)
Diploma	27	(9.9%)
Bachelor	70	(25.5%)
Masters	3	(1.1%)
PhD	1	(0.4%)
Marital status		
Married	244	(89.1%)
Not married	30	(10.9%)
Occupation		
Non-high risk occupations	264	(96.3%)
High risk occupation	10	(3.7%)

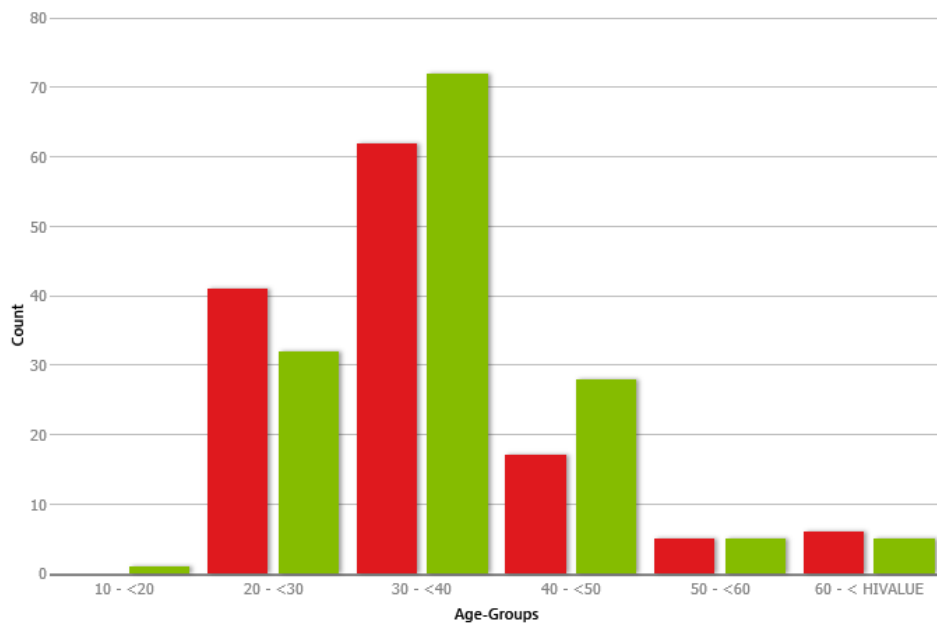


Figure 4.2 Age distribution of participants

Blood donation was found to be the most common way in which HBV was diagnosed in males (44%), while antenatal screening was the most common means of diagnosis in females (47%). Blood test for other reasons (e.g. after birth, after surgery, abdominal pain, multi transfusion screen, health check-up) was the second most common source of diagnosis in both genders. The least common means of diagnosis in both genders was contact screening (Table 4.2).

Table 4.2 HBV means of diagnosis

Means of diagnosis	Gender	
	male	female
Antenatal screening	0(0%)	61(47%)
Blood donation	63(44%)	10(8%)
Blood test	50(35%)	38(29%)
Symptomatic	9(6%)	7(5%)
Family screening or sexual contact screening	2(1%)	2(2%)
Pre-employment test	7(5%)	11(8%)
Others	12(8%)	2(2%)

Table 4.3 summarizes the prevalence of HBV transmission risk factors grouped as behavioural risk factors, perinatal and household contact or nosocomial risk factors. The result of each group is presented in more details in Tables 4.4, 4.5 and 4.6.

It is apparent that high risk behaviours were very common in this study population with similar distribution in the two age groups. Almost two thirds of the participants had histories of perinatal and household contact transmission risks which were more common in those under the age of 28 years. 60.2% of the interviewees had at least a history of nosocomial risks. Only one participant reported no history of HBV acquisition risk factors.

Table 4.3 Prevalence of HBV transmission risk factors in this study group

Frequency of risk factors	Total (n=274)	CI	Age 13-28 yr (n=62)	CI	Age >28 yr (n=212)	CI
Behavioural risk factors	269(97.8%)	96.8-99.6	61(98.4%)	96.8-100	208(97.6%)	95.5-99.7
Lack of knowledge about hepatitis B	225(82.1%)	77.0-87.1	44(71.0%)	57.6-84.4	181(5.4%)	2.5-8.7
Family related risk factors	177(64.6%)	57.5-71.6	45(72.6%)	59.6-85.6	132(62.3%)	58.1-66.5
Nosocomial risk factors	165(60.2%)	67.6-52.8	35(56.5%)	48.1-64.9	130(61.3%)	52.9-69.7
No risks	1(0.4%)	-5.3-7.3	0(0%)		1(0.5%)	-6-7.5

Table 4.4 shows the frequency of nosocomial risk in this study population which appear to be low. The majority of participants had no history of surgery (70.4%), hospitalization (71.9%), blood transfusion (91.2%) and endoscopy (93.4%). Only one patient had a history of dialysis and none of the participants had a history of organ transplantation. With further statistical analysis, significant difference in the frequency of endoscopy between age groups was noted, but the number of participants in the 13-18 years was smaller than that in the two remaining age groups. The Chi-square test did not show any significant difference in the frequency of other nosocomial risk factors between sex, age and educational level.

When trying to assess the effect of perinatal, early horizontal and spousal transmission of HBV among participants (Table 4.5), more than half of the participants had a positive family history of HBV infection (father, siblings or cousins). This was significantly different between sexes, $P < 0.02$ and educational level $P = 0.0019$. Significant difference was also found between the three age groups (<23, 24-28, >28) in mothers' HBV positivity (33.3%,

14.3%, 6.6% respectively, $P < 0.05$). Contact with HBV infected persons appeared to be statistically significantly difference in different educational levels $P < 0.05$.

Table 4.6 shows the prevalence of high risk behaviours in the participants. A minority of participants indicated histories of tattoos (0.4%), acupuncture (1.5%), traditional phlebotomy (5.1%), extra-marital sexual contact (8.8%) and circumcision in non-clinical settings (13.5%). The frequency of circumcision in non-clinical settings decreased significantly by the increase in educational levels ($P = 0.04$). Unawareness about HBV infection (82.1%), piercing in non-clinical settings (46.7%), regular shaving with a barber (46.7%), *wasam* (49.6%) were more common in this studied group. There was a significant association of hepatitis B and age groups, and educational levels ($P < 0.05$ and $P < 0.001$ respectively). The relation between having *wasam* and gender, age or educational level was also significant ($P < 0.02$, $P < 0.05$, $P = 0.03$ respectively).

Table 4.4 Frequency of nosocomial risk factors by gender, age and educational level.

Nosocomial risk factors	Total (n=274)	gender		Age			Educational level		
		Male(n=143)	Female(n=131)	13-23 (n=6)	24-28 (n=56)	>28 (n=212)	Pre- secondary (n=61)	Secondary (n=112)	Post- secondary (n=101)
Surgery	81(29.6%)	37(25.9%)	44(33.6%)	4(66.7%)	16(28.6%)	61(28.8%)	21(34.4%)	36(32.1%)	24(23.8%)
Hospitalization	77(28.1%)	42(29.4%)	35(26.7%)	3(50.0%)	13(23.2%)	61(28.8%)	18(29.5%)	25(22.3%)	34(33.7%)
Blood transfusion	24(8.8%)	13(9.1%)	11(8.4%)	0(0%)	5(9.0%)	19(9.0%)	7(11.5%)	12(10.7%)	5(5.0%)
Endoscopy*	18(6.6%)	11(7.7%)	7(5.3%)	2(33.3%)	2(3.6%)	14(6.6%)	8(13.1%)	6(5.4%)	4(4.0%)

**the frequency of endoscopy shows statistical difference between age groups, $\chi^2 = 7.8227$, d.f. = 2, $P < 0.02$*

Table 4.5 Frequency of family related risk factors by gender, age and educational level

Risk factors	Total (n=274)	gender		Age			Educational level		
		Male(n=143)	Female(n=131)	13-23 (n=6)	24-28 (n=56)	>28 (n=212)	Pre- secondary (n=61)	Secondary (n=112)	Post- secondary (n=101)
Maternal history of HBV				*					
yes	24(8.8%)	8(5.6%)	16(12.2%)	2(33.3%)	8(14.3%)	14(6.6%)	2(3.3%)	13(11.6%)	9(8.9%)
No	100(36.5%)	52(36.4%)	48(36.6%)	3(50.0%)	18(32.1%)	79(37.3%)	22(36.1%)	39(34.8%)	39(38.6%)
Unknown	150(54.7%)	83(58.0%)	67(51.2%)	1(16.7%)	30(53.6%)	119(56.1%)	37(60.7%)	60(53.6%)	53(52.5%)
Family history of HBV		**					**		
Yes	150(54.7%)	67(46.8%)	83(63.4%)	4(66.6%)	36(64.3%)	101(51.9%)	19(31.1%)	65(58.1%)	66(65.3%)
No	61(22.3%)	35(24.5%)	26(19.8%)	1(16.7%)	8(14.3%)	52(24.5%)	21(34.4%)	24(21.4%)	16(15.8%)
Unknown	63(23.0%)	41(28.7%)	22(16.8%)	1(16.7%)	12(21.4%)	50(23.6%)	21(34.4%)	23(20.5%)	19(18.8%)
Contact with HBV infected person		***					***		
Sexual contact	31(11.3%)	11(7.7%)	20(15.3%)	1(16.7%)	8(14.3%)	22(10.4%)	4(6.6%)	16(14.3%)	11(10.9%)
Non-sexual contact	117(42.7%)	54(37.8%)	63(48.1%)	2(33.3%)	27(48.2%)	88(41.5%)	16(26.2%)	51(45.5%)	50(49.5%)
No contact	95(34.7%)	58(40.6%)	37(28.2%)	2(33.3%)	12(21.4%)	81(38.2%)	28(45.9%)	35(31.3%)	32(31.7%)
Unknown	31(14.0%)	20(16.1%)	11(8.4%)	1(16.7%)	9(16.1%)	21(9.9%)	13(21.3%)	10(8.9%)	8(7.9%)
Family history of liver disease									
Yes	27(9.9%)	13(9.1%)	14(10.7%)	2(33.3%)	8(14.3%)	17(8.0%)	4(6.6%)	10(8.9%)	13(12.9%)
No	199(72.6%)	102(71.3%)	97(74.0%)	3(50.0%)	36(64.3%)	160(75.5%)	41(67.2%)	85(75.9%)	73(72.3%)
Unknown	48(17.5%)	28(19.6%)	20(15.3%)	1(16.7%)	12(21.4%)	35(16.5%)	16(26.2%)	17(15.2%)	15(14.9%)

* significant difference in mother's history of HBV infection by age, $\chi^2=9.5164$, d.f. = 4, $P < 0.05$

** significant difference in family history of hepatitis B by gender, $\chi^2=9.0944$, d.f. = 3, $P < 0.02$ and educational level $\chi^2=20.9362$, d.f. = 6, $P = 0.0019$

*** living with HBV infected persons significantly differed between the three educational level groups ($\chi^2=19.1856$, d.f. = 6, $P < 0.05$)

Table 4.6 Frequency of high risk behaviours by gender, age and educational level

High risk behaviours	Total (n=274)	gender		Age			Educational level		
		Male(n=143)	Female(n=131)	<23	23-28	>28	Pre-secondary (n=61)	Secondary (n=112)	Post-secondary (n=101)
Lack of knowledge of HBV infection	225(82.1%)	119(83.2%)	106(80.9%)	*			*		
Piercing in non-clinical settings	128(46.7%)	15(10.5%)	113(86.3%)	4(66.7%)	40(71.4%)	181(85.4%)	60(98.4%)	90(84.8%)	70(69.3%)
Regular shaving with a barber	128(46.7%)	128(88.8%)	-	3(50.0%)	21(37.5%)	104(49.1%)	33(54.1%)	48(42.9%)	47(46.5%)
Cautery(Wasam)**	128(46.7%)	128(88.8%)	-	2(33.3%)	22(39.3%)	104(49.1%)	25(40.9%)	54(48.2%)	49(48.5%)
Traditional phlebotomy	132(49.6%)	75(52.4%)	61(46.6%)	1(16.7%)	21(37.5%)	114(53.8%)	39(63.9%)	55(49.1%)	42(41.6%)
Acupuncture	14(5.1%)	6(4.2%)	8(6.1%)	1(16.7%)	3(5.4%)	10(4.7%)	5(8.2%)	5(4.5%)	4(4.0%)
Circumcision in non-clinical settings	4(1.5%)	1(0.7%)	3(1.7%)	0(0%)	0(0%)	4(1.9%)	2(3.3%)	0(0%)	2(1.9%)
Extramarital sexual contact	37(13.5%)	37(25.9%)	-	0(0.0%)	2 (3.6%)	35(16.5%)	***		
IDU	24(8.8%)	24(16.8%)	0(0%)	1(16.7%)	2(3.6%)	21(9.9%)	12(19.7%)	16(14.3%)	9(8.9%)
	-	-	-	6(9.8%)	11(9.8%)	7(6.9%)	-	-	-

*Significant difference in hepatitis B awareness by age and educational level ($\chi^2= 6.8664$, d.f. = 2, $P <0.05$) and ($\chi^2= 22.8042$, d.f. = 2, $P <0.001$) respectively.

** Significant difference in wasam by gender, age and educational level ($\chi^2= 7.0807$, d.f. = 2, $P <0.02$), ($\chi^2= 10.5833$, d.f. = 4, $P <0.05$), ($\chi^2= 10.5394$, d.f. = 4, $P =0.03$) respectively.

*** Significant difference circumcision between the three educational groups ($\chi^2= 13.0917$, d.f. = 6, $P =0.04$)

4.6 Discussion:

Research to determine the major risk factors for transmitting HBV in Oman has been lacking. This survey was conducted to determine the prevalence of major risk factors for acquiring hepatitis B infection among Omani patients positive for hepatitis B surface antigen. As there has not been a control group in this study, it is not possible to assess the causative role of risk factors for HBV acquisition in Oman. However, the results of this study will provide further understanding of the epidemiology of hepatitis B in Oman and it will aid in identifying the people who are at higher risk of acquiring HBV.

There were several key findings from this survey. These include; similar numbers of male and female patients with the majority aged 20 – 39 years. The geographic distribution of the participants surveyed reflects that of the general population. Antenatal screening is found to be the most common method by which the female participants were diagnosed with hepatitis B. This is in contrast to males in whom blood donation was reported to be the most common method of diagnosis. As for HBV transmission risk factors, nosocomial risk factors were less common in this group of patients than intrafamilial and behavioural risks. Knowledge about HBV infection was scarce among our participants.

There are some strengths and weaknesses in this study. One of the strengths is the use of a standard questionnaire containing closed questions throughout the study. The same interviewer filled all the questionnaires during a direct interview with the participants for consistency. This way, any misinterpretations of questions by patients were corrected at the time of the interview thus minimizing any false reporting. Moreover, any potential heterogeneity in reporting that may have arisen from using two interviewing methods (face to face vs. telephone) would be expected to be minimised. Another strength is that both hospitals screen pregnant women for HBsAg, this would give a more accurate representation of hepatitis B distribution between genders.

The limitations of this study might arise from referral bias and recall error. Referral bias from recruiting patients from tertiary referral hospitals, SQUH and AFH, could play a role in this study. Patients under the age of 13 years are not seen at the outpatient clinics where patients were recruited for this study. This would limit our investigations regarding vertical transmission of HBV and would make the findings of this study only applicable to adults in Oman. In addition, as both hospitals are located in Muscat Governorate, patients from regions outside Muscat are underrepresented. This was noted for Dhofari patients. Only 0.7% of our

participants came from Dhofar Governorate, while CDSC reports show that Dhofar governorate accounted for almost a quarter of the cumulative incidence of AHB from 1991 to 2010 (Sultanate of Oman Ministry of Health, 2012). Risk factors for HBV transmission might differ in Dhofari patients compared to the general population.

In any study in which data is collected during an interview with the patients, recall error is expected to occur especially in patients with chronic infection, patients diagnosed with the disease a long time ago and older patients who have a long history. Patients may report that an exposure (risk factor) preceded the outcome (hepatitis B) even if it actually occurred after, hence, overestimating the role of these risk factors in this group of patients. Using the date of diagnosis as the reference date helped to minimise this recall error. In addition, risk factors such as sexual activity or intravenous drug use are difficult to investigate and may be underestimated due to the sensitivity of these issues culturally and religiously in Oman.

The male to female ratio was almost equal to one. This finding is consistent with other studies conducted in Oman (Al-Naamani et al., 2013) and Iran (Alavian et al., 2012) (Merat et al., 2009). On the other hand, men account for most of HBV cases in most parts of the world (Abdo et al., 2012a) (Memish et al., 2010) (Robinson et al., 2005) (Custer et al., 2004) (Alswaidi and O'Brien, 2010) (Toukan and Group, 1990) (Custer et al., 2004) (Centers for Disease and Prevention, 2004) (World Health Organization, 2002 #25). It may be that Oman has a different epidemiology of hepatitis B or this might be a result of referral bias. Patients were diagnosed from antenatal screening for females and blood donation for males in similar proportions (47% vs. 44%).

Almost three quarters of the participants lie in the 20 – 39 age group. Generally, this would contribute indirectly to economic burden associated with job loss, reduced work productivity and premature death (Yang et al., 2001). Specifically, most of the female patients were of child-bearing age which maintains the risk of mother to child transmission of hepatitis B.

Iatrogenic risk factors seemed to be the least frequent among our participants. Almost one third of participants have a history of surgery, which was the most prevalent nosocomial risk factor. A case-control study from Iran, which has a similar hepatitis B prevalence to Oman, found that a history of surgery is an independent risk factor for CHB carriage (Jahangirnezhad, 2011). On the contrary, studies conducted in Arab and African countries showed insignificant role of surgical interventions in transmitting HBV (Gasim et al., 2013). Therefore, it is difficult to assess the real impact of surgical interventions in transmitting

hepatitis B. None of the participants reported any history of organ transplantation or haemodialysis. This may be because the majority of participants were of young age, whereas such treatments are usually associated with end stage disease occurring later in life. It may also reflect the sample size and particular clinic populations.

Intra-familial transmission of hepatitis B can be through vertical or horizontal mode by either sexual or non-sexual contact. The latter is thought to be the predominant mode of hepatitis B transmission in the Middle East. (Toukan and Group, 1990). In the current sample, only 8.8% of participants reported positive mother status for HBV which was significantly associated with the age of participants ($p < 0.05$), while more than half of the participants reported familial contact with HBV positive persons (11.3% sexual contact vs. 42.7% non-sexual contact). The majority of the participants who reported sexual contact also have siblings with HBV. This suggests the possibility of the infection occurring earlier in life. HBV is a highly infective virus and HBeAg is most prevalent in children, a fact which is associated with the high infectivity rate (Toukan and Group, 1990). Shared use of contaminated materials such as razors, tooth brushes, towels, eating utensils may account for early horizontal transmission of HBV among family members (Urganci et al., 2013) (Alswaidi and O'Brien, 2010) (Toukan and Group, 1990) while the availability of sanitisation tools within the household are reported to be protective against transmission (Ben-Alaya-Bouafif et al., 2010). Contact with an HBV positive person was found to be significantly associated with the participants' educational level ($p < 0.05$), which reflects the socio-economic status of the individual. Although lower educational level and lower income are identified risk factors for HBsAg positivity in both high and intermediate endemicity regions (Zhang et al., 2013) (Merat et al., 2009), we found higher contact with HBV positive patients reported by higher education groups. This might be because highly educated persons are more likely to know about the health status of their family members.

From this survey, high-risk behaviours were noted to be common in this group of patients. The majority of females had piercing in non-clinical settings and a similar proportion of males shaved regularly with barbers. Determining the role of these practices in transmitting HBV is difficult as it is poorly researched within the region. Although body piercing has been identified as a potential risk factor for HBV infection (Zhang et al., 2013) (Zhang et al., 2008), a recent study in the Netherlands found that body piercings did not increase the risk of HBV infection for the Dutch population (Urbanus et al., 2011). While this may be true for the Netherlands where HBV endemicity is low and hygiene guidelines have been introduced in

piercing shops, in Oman HBV is more endemic and most of our participants had their piercings at home. Moreover, piercings for females are usually done at a young age in Oman where the risk of chronic carriage is higher (Goldstein et al., 2005).

With respect to barber practices, studies from the Middle East showed barbers had low to moderate awareness that hepatitis can be transmitted by contaminated razors, and 46% of shaves were done with reused razors (Ali et al., 2009) (Al-Rabeei et al., 2012). HBV DNA was detected in 6.6% of used razor blades and cuts from barbershops are associated with HBV transmission with an odd ratio of 4.74 (Eroglu et al., 2010) (Alswaidi and O'Brien, 2010). Despite the effort of the Omani government to ensure the safety of these practices by requiring the availability of sanitization areas and tools in all barber shops with regular inspection, their contribution to HBV transmission cannot be ruled out entirely.

None of the participants in our study reported a history of intravenous drug use and only 16.8% reported multiple sexual partners. Such risk factors are the most common modes of HBV transmission in lower endemicity regions in Western societies. In the USA, sexual contact (heterosexual or homosexual) and IDU account for 40.9% and 18.2% of AHB respectively (Goldstein et al., 2002). In China, on the other hand, where HBV is of high endemicity, no association between AHB and sexual contact or IDU was found in univariate and multivariate regression analyses (Zhang et al., 2008). The reason for this may be the similar attitude of Chinese and Omani people towards these behaviours. Studies in the Middle East reported that HBV prevalence among IDU ranges between 6% to 44.3% (Ali et al., 2009) (Jahangirnezhad, 2011).

Antenatal screening seems to be one of the most effective detection strategies for women in our sample and almost half of the female participants were discovered to be HBsAg positive during pregnancy. Despite the evidence of higher prevalence of HBV infection among Omani pregnant women (7.1%) compared to those in other GCC states (Saudi Arabia 1.6%, UAE 1.5% and Qatar 1%) (Al Awaidey et al., 2006) (Gasim et al., 2013), antenatal screening for HBsAg is not available at *MoH* institutes. With the introduction of neonatal vaccination in 1990, it would take around 20-40 years for the vaccine alone to eliminate vertical transmission of HBV in Oman. The *Royal Australian and New Zealand College of Obstetrics and Gynaecology* recommends routine screening of all pregnant women for HBsAg, and the administration of active and passive vaccination for infants born to HBsAg positive mothers (Troung and Walker, 2013). These measures are associated with 90-100% effectiveness in

preventing the transmission of the virus in neonates born to mothers with HBV infection (Hu et al., 2012) and should consider in Oman. However, in mothers positive for HBeAg with high viral load, post prophylaxis failure is possible and treatment within the third trimester should be considered. Anti-viral therapy with lamivudine for pregnant women with abnormal ALT levels, positive for HBsAg and HBeAg, have HBV DNA $\geq 1.0 \times 10^7$ copies/mL, during the gestation period between 24-32 weeks, decreases intrauterine HBV infection along with the vaccine and immunoprophylaxis for the new-born babies (Yu et al., 2012).

Despite the evidence of common contact with HBV positive family members among the participants, only 1.5% were diagnosed from contact screening. This suggests that contact screening is not being widely applied. Greater focus on contact screening could aid in the control of HBV infection in Oman by identifying non-immune contacts and vaccinating them. Furthermore, it could act as a secondary prevention measure by identifying those with chronic infection, providing them with the appropriate treatment or follow up and hence, reduce the long term complications (cirrhosis or HCC) and mortality associated with chronic infection.

The majority of our participants had no knowledge about HBV infection prior to their diagnosis. Educating individuals about hepatitis B risk factors could help to reduce the risk of spreading the virus. It has been shown that improving awareness regarding risk factors of HBV transmission has led to a decrease in HBV prevalence in Iran (Alavian et al., 2007).

In conclusion, this study indicated that risk factors for HBV infection in Oman include direct contact of infected individuals within a family and exposure to high-risk behaviours such as piercing and barber shaving. While further analytical epidemiological studies are needed to assess the proportion of hepatitis B attributable to different risk factors, implementing antenatal screening for pregnant women would reduce the vertical transmission of HBV, and improving contact screening would reduce horizontal transmission of the virus and reduce morbidity and mortality associated with the virus. Future work is required to confirm the association with behavioural risk factors, mainly piercing and shaving at barber shops, and enhance interventions aimed at reducing the risk of horizontal transmission.

5 THE CONTRIBUTION OF HEPATITIS B TO LIVER CIRRHOSIS IN OMAN.

5.1 Introduction:

Chronic infection with HBV occurs mainly in patients acquiring the infection at young age either vertically or during early childhood. Cirrhosis of the liver and primary liver cancer are associated with the long exposure to HBV.

Despite the strong association of HBV with so many cases of liver cirrhosis and HCC, there is no available literature looking at the role of HBV in relation to liver cirrhosis in Oman. Such an estimation would contribute to understanding of the burden of this infection in Oman. Further understanding of the hepatitis B outcomes will encourage public health measures to reduce the burden of long term consequences of CHB.

The study outlined in this chapter aims to estimate the contribution of HBV infection to cirrhosis in Oman.

5.2 Methods:

Identifying patients:

The study was conducted in two tertiary hospitals in Oman which are; the *Sultan Qaboos University hospital* (SQUH) and the *Armed Forces Hospital* (AFH). Cirrhotic patients were identified differently in the two hospitals. From SQUH, a list of patients diagnosed with either “Other or Unspecified Cirrhosis of Liver”, “Fibrosis and Cirrhosis of Liver”, “Alcoholic Cirrhosis of Liver” was provided by the Hospital Information System. The list contained the patients’ names, gender, date of birth and medical record number. Duplicates were removed and data of interest was collected from the patients’ computerized medical records.

At AFH, cases were identified manually by going through the Admission and Discharge books from all the wards admitting medical cases. These wards include the green ward (male patients), the red ward (female patients) and the gold ward 1 (VIP cases). These books were dated from December 2006 till April 2012 from green ward and from January 2006 till July 2012 from red ward. The Admission and Discharge book for the year of 2007 was not found from red ward. Gold ward 1 is a new ward and the admission and discharge book dated from March 2012 till April 2013. From those books, patient ID was collected for any cases

admitted for any gastrointestinal reason (e.g. abdominal pain, hematemesis, OGD, ascetic tap, upper GI bleed, hepatic encephalopathy, ascites, HCC, hepatitis, cirrhosis, alcohol withdrawal). The electronic medical records of those patients were checked through the Hospital Information System for the specific diagnosis of liver cirrhosis.

Inclusion criteria:

All cirrhotic patients that could be identified with computerized records from 2006-2013 from SQUH and AFH were included.

Exclusion criteria:

Patients where a specific diagnosis of cirrhosis was not made, duplicated cases, those with incomplete computerized medical records (no radiology or biopsy data to confirm the diagnosis), non-cirrhotic portal hypertension (e.g. schistosomiasis, PV thrombosis) and non-cirrhotic cases were excluded from this study.

Data collected:

The most recent electronic data of each patient was collected. The data collected included demographic data (age and gender). Moreover, data regarding abdominal radiology (Ultrasound, CT scan and/or MRI), OGD, liver biopsy, biochemical data (ALT, AST, bilirubin, albumin), and hematological data (INR or PT and platelet count) were also collected to confirm the diagnosis of cirrhosis. HBV and HCV viral markers were collected to assess the contribution of these viral infections to cirrhosis. These markers were; HBsAg, ant-HBs, HBcAg, anti-HBc, HBeAg, anti-HBe, HBV DNA, HCV antibody, HCV RNA. Other data representing alpha 1 antitrypsin levels, serum copper levels, ferritin levels, autoimmune profile, antinuclear antibody and patients' medical history (drug history, diabetes mellitus, family history of liver disease, Nonalcoholic Steatohepatitis (NASH)) and social history (smoking and alcohol consumption) were also collected to assess other etiologies of cirrhosis.

Analytical methods:

Confirming the diagnosis of cirrhosis:

The histological findings of cirrhosis on biopsy is the gold standard for diagnosis (Chen et al., 2007). However, this procedure is invasive and only 9% of the studied sample had undergone

biopsy. Radiological tests, on the other hand, were more common in this studied cohort. Radiological findings (US, CT and MRI) are not very sensitive in detecting cirrhosis; however, they are highly specific when the cause is known (74.1% and 84% respectively) (Lin et al., 1993) (Schuppan and Afdhal). Therefore, the use of radiological findings in the diagnosis of cirrhosis in this study is objective.

Patients were classified into three different groups depending on the degree of certainty of the diagnosis. The three groups are definite cirrhosis, probable cirrhosis and possible cirrhosis. The diagnosis was based on histological, radiological (ultrasonography (US), Computed Tomography (CT) scan or Magnetic Resonance Imaging (MRI)) and laboratory tests (biochemical and haematological). Table 5.1 describes the criteria used in classifying the patients to each category.

Table 5.1 Categories depending on the accuracy of cirrhosis diagnosis

Category	Basis of diagnosis
Definite cirrhosis	<ul style="list-style-type: none"> • <i>Either</i> presence of histological features of cirrhosis which include: bridging fibrous septa, parenchymal nodules and disruption of the liver architecture. (Kumar and Robbins, c2007) • <i>And/ or</i> irregular or undulated liver surface with heterogeneous or coarse echotexture on radiological images. Positive extrahepatic features such as enlarged spleen, collateral vessels, ascites and dilated PV.(Schuppan and Afdhal) • <i>With/ without</i> biochemical tests showing raised aminotransferases (with AST>ALT usually), raised bilirubin, decreased albumin. Haematological tests showing decreased platelet count and increased INR or PT. (Braunwald and Eugene, c2001.)
Probable cirrhosis	<ul style="list-style-type: none"> • <i>Either</i> irregular or undulated liver surface or heterogeneous or coarse echotexture on radiological images. <i>With or without</i> extrahepatic features such as enlarged spleen, collateral vessels, and ascites and dilated PV. • <i>With/ without</i> biochemical tests showing raised bilirubin and decreased albumin. Haematological tests showing decreased platelet count or increased INR or PT
Possible cirrhosis	<ul style="list-style-type: none"> • Biochemical tests show raised bilirubin, decreased albumin. Haematological tests showing decreased platelet count or increased INR or PT but no histological or radiological tests to confirm the diagnosis.

Aetiology of cirrhosis:

The etiology of cirrhosis was based on the specified diagnosis reported in the patients' record with the aid of laboratory findings. aetiologies were classified as HCV, HBV, Alcoholic, cryptogenic, HBV and HCV co-infection, auto-immune, Budd-Chiari, NASH and not-otherwise specified. Etiologies that were uncommon in this studied population were classified as others. These included cardiac cirrhosis, primary biliary cirrhosis, primary sclerosing cholangitis, secondary sclerosing cholangitis, biliary atresia, amiodarone induced cirrhosis, Fanconi syndrome and Wilson's disease.

There were 16 patients diagnosed as Alcohol and HCV related cirrhosis and four patients diagnosed as Alcohol and HBV related cirrhosis. However, those patients were added to the HCV or HBV categories. This is because alcohol consumption is measured subjectively by the doctor in Oman as no specific unit is used.

Interpretation of virological markers:

Patients with hepatic viral aetiologies were grouped depending on the status of their viral markers. Positive anti-HBc indicates current or previous infection with HBV. Positive HBsAg indicates current infection with HBV. On the other hand, patients positive for anti-HBc but negative for HBsAg are considered to have had past infection. Positive HCV anti-bodies (HCV AB) status and positive anti-HBc indicate co-infection of HBV and HCV. Our definition of was based on the positivity of anti-HBc (rather than HBsAg) because HBsAg expression is usually decreased in HCV patients (Lok and McMahon, 2007) (Shih et al., 1993) (Uchida et al., 1997). Patients with positive HCV AB alone were grouped in the HCV mono-infection group.

Immunity against HBV is determined by the presence of anti-HBs. Cirrhotic patients were classified as either immune, non-immune or with unknown immunity status. Immune patients are those with positive anti- HBs, and depending on their anti- HBc status, they were further classified as immune due to previous infection (anti-HBc positive), immune by vaccine (anti-HBc negative) and immune due to unknown reason (anti-HBc unavailable). Non-immune patients are those with negative anti- HBs status. Unknown immunity status is for patients where the anti-HBs status is not available. This calculation excluded patients who were positive for HBsAg as, clearly, they are non-immune.

Statistical analysis:

Data was originally collected on Microsoft Excel 2010. However, all statistical analysis was done using Epi info version 7. This included calculating the frequencies of cirrhosis etiology, calculating the median values of age and laboratory data.

5.3 Results:

Out of 469 patients identified with cirrhosis from both hospitals, 419 met the criteria and were included in the final analysis. When categorised depending on diagnosis accuracy, 70.9%, 10.3%, 18.8% of the study population had definite, probable or suspected cirrhosis respectively (figure 5.1).

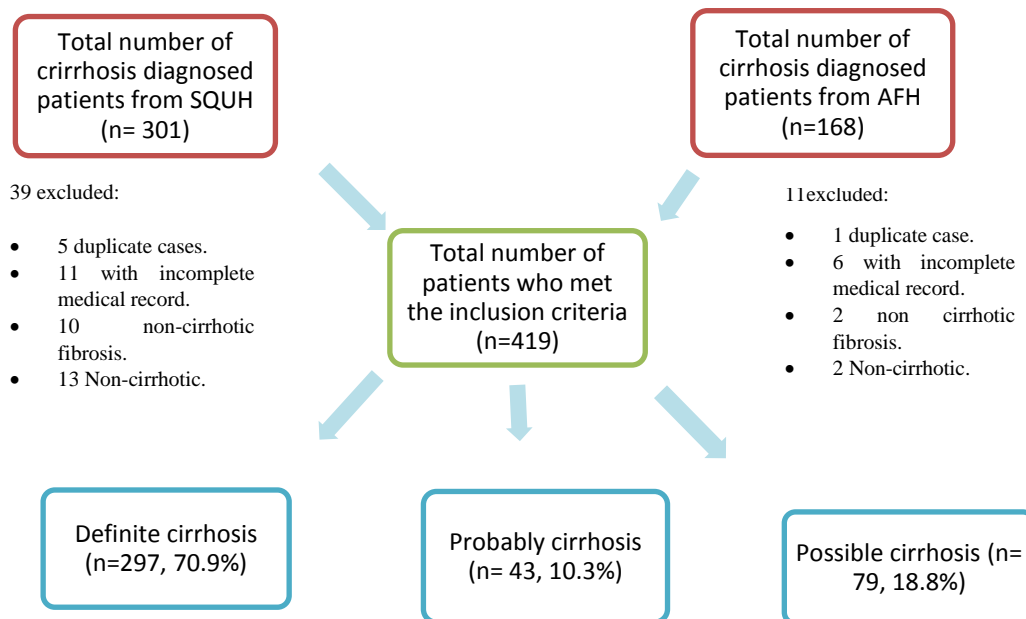


Figure 5.1 Flow chart showing the results of patients selection process

The demographic characteristics are shown in table 5.2. Two thirds of cirrhotic patients were males. The youngest patient was 5 years old and the oldest was 95. The median age of the study sample was 59 years. The majority (97.1%) of cirrhotic patients were Omanis. Almost half of the group was also diabetic and more than a fifth had indicated consumption of alcoholic beverages. It is worth noting that there was a significant amount of missing data for this study population. For example, 89% of family history for liver disease was missing.

Table 5.2 Patients' demographics and clinical history

Variables	Number	Percentage
General demographic profile		
No. of patients	419	
Age (years; median)	59	
Gender		
Male	283	(67.5%)
female	136	(32.5%)
Ethnicity		
Omani	407	(97.1%)
Non-Omani	12	(2.9%)
Patients' history		
Diabetes mellitus		
Yes	200	(47.7%)
No	59	(14.1%)
Not available	160	(38.2%)
Family history of liver disease		
Yes	15	(3.6%)
No	31	(7.4%)
Not available	373	(89%)
Alcohol consumption		
Yes	93	(22.2%)
No	86	(20.5%)
Not available	240	(57.3%)
Smoking		
Yes	58	(13.8%)
No	84	(20%)
Not available	277	(66%)

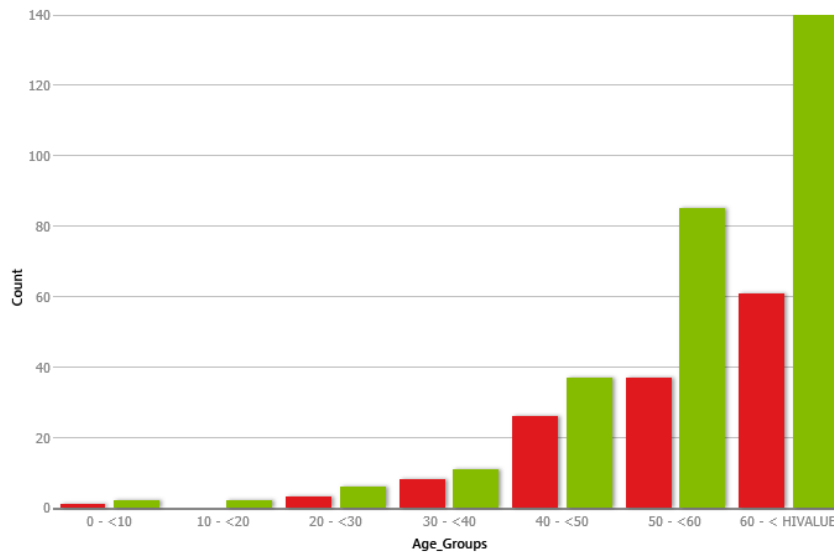


Figure 5.2 Age distribution of cirrhotic cases

The aetiologies of cirrhosis according to diagnosis in medical records are summarised in Table 5.3. It shows that HBV infection accounted for 24% of patients with cirrhosis in this sample. When stratified by gender, HBV related cirrhosis was more common in males than females (29% vs. 13% respectively, $p < 0.01$), while HCV related cirrhosis was more common in females than males (43% vs. 24% respectively, $p < 0.01$). Only 2% of the studied population had co-infection with HCV and HBV, and 1% had HBV and alcohol related cirrhosis.

Table 5.3 Aetiology of cirrhosis stratified by gender (diagnosis per patients' medical records).

Aetiology of cirrhosis	Entire cohort (n=419)		Male (n=283)		Female (n= 136)	
	No.	(%)	No.	(%)	No.	(%)
HCV related cirrhosis	128	(31%)	69	(24%)	59	(43%)
HBV related cirrhosis	99	(24%)	81	(29%)	18	(13%)
Alcohol related cirrhosis	49	(12%)	46	(16%)	3	(2%)
Cryptogenic cirrhosis	44	(11%)	22	(8%)	22	(16%)
HBV and HCV co-infection	7	(2%)	6	(2%)	1	(1%)
AIH related cirrhosis	7	(2%)	2	(1%)	5	(4%)
NASH	3	(1%)	3	(1%)	-	
Budd-Chiari	3	(1%)	3	(1%)	-	
Others*	10	(2%)	7	(2%)	3	(2%)
Not otherwise specified	69	(16%)	44	(16%)	25	(18%)

*Others included the uncommon etiologies of liver cirrhosis in this study cohort. These were: two cardiac cirrhosis, two primary biliary cirrhosis, one primary sclerosing cholangitis, one secondary sclerosing cholangitis, one biliary atresia, one amiodarone induced cirrhosis, one Fanconi syndrome and one Wilson's disease.

Table 5.4 shows the distribution of hepatic virological markers in this population of cirrhotic patients. More than half had evidence of previous or current infection with HBV. Current infection with HBV was slightly more common than HCV mono-infection (19.8% vs. 17.9%). Serological data showed higher rates of HBV and HCV co-infection than identified from patients' notes (table 5.3). In the HBV positive group (anti-HBc +), 34% achieved HBeAg seroconversion and only 3.3% remain positive for HBeAg. There were 7 patients with occult HBV infection i.e. patients were positive for HBV DNA but negative for HBsAg (data not presented).

Table 5.4 HBV and HCV status of the study cohort

Definition	Number (%)	Serologic findings
Current or previous HBV infection*	215 (51.3%)	Positive anti-HBc
Current infection with HBV	83 (19.8%)	Positive HBsAg
Previous HBV infection (with or without immunity development)	77 (18.4%)	Positive anti-HBc with negative HBsAg and/or anti-HCV (with or without positive anti-HBs)
Concurrent infection with HBV and HCV	53 (12.6%)	Positive anti-HBc and HCV AB
Current mono-infection with HCV	75 (17.9%)	Positive HCV AB

*Note that there are two extra patients in this group which is attributed to the unknown virological status in some patients.

Table 5.5 summarises the most recent laboratory data of the 419 cirrhotic patients by virological status. Cirrhotic patients found positive for HBsAg were the youngest of the groups. The male to female ratio was highest in patients currently infected with HBV (4.2) and lowest in patients currently infected with HCV (1.3).

In general aminotransferases were elevated in all the groups, with AST being higher than ALT. In addition, elevated bilirubin and decreased albumin was noticed in all groups. Haematological tests show decreased platelet count in all groups with it being lowest in HBsAg + infected group ($100 \times 10^9/L$). INR and PT were almost equally elevated in all groups.

Table 5.5 Background and laboratory data of patients with or without viral hepatitis.

Laboratory values	Entire cohort	HBV positive patients		Co-infection	HCV positive patients (anti-HCV +)
		(HBsAg+)	(HBsAg-/ Anti-HBc+)	with HBV and HCV (anti-HCV+/ Anti-HBc+)	
Demography					
No. of patients	419	83	77	53	75
Age (median (range))	59(5-95) 2(283/136)	56(35-83) 4.2(67/16)	61(5-95) 1.9(51/26)	57(23-85) 1.5(32/21)	59(7-94) 1.3(43/32)
Sex ratio(M/F)					
Biochemical tests (median (range))					
AST (IU/mL)	76(10-14335)	76(19-7582)	70(10-1800)	75(17-14335)	73(15-2152)
ALT(IU/mL)	41(0-4180)	39(12-4180)	45(0-610)	45(10-3733)	38(9-634)
Albumin	26(10-78)	24(12-44)	25(10-45)	25(10-49)	27(13-78)
Bilirubin	48.4(2-753)	39(6-659)	51.4(4.9-564)	46(3-416)	62(3.9-753)
Haematological tests (median (range))					
Platelets count (×109/L)	105(13-513)	100(15-331)	107(30-513)	113(21-489)	109(14-462)
INR (secs)	1.5(0.9-46)	1.5(0.9-7.5)	1.5(1-4.1)	1.6(1-19)	1.4(0.9-9.4)
PT (secs)	18(10.2-100)	19.4(13.6-40.9)	19(10.2-100)	16.7(11-53.9)	18(11.8-36)

Figure 5.3 shows that 36% of patients were immune (positive anti-HBs) against HBV with the majority (27%) being immune due to previous infection (anti-HBs +/anti-HBc +), 5% immune by vaccination (anti-HBs +/anti-HBc -) and 4% immune by unknown method (anti-HBs +/anti-HBc unknown). 34% of the studied cohort are un-immune (anti-HBs -), and 30% have unknown immunity status.

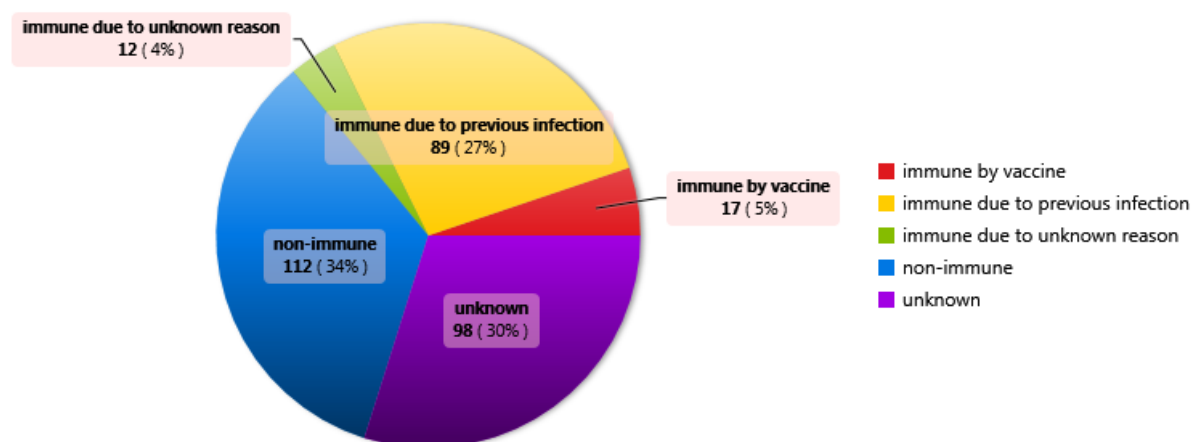


Figure 5.3 HBV immunity status of non HBsAg + cases (n=328)

5.4 Discussion:

This was a cross sectional study conducted in order to estimate the contribution of hepatitis B to liver cirrhosis in Oman. The study revealed that the median age of cirrhotic patients was 59 years and males accounted for two thirds of the total studied population. Most patients were of Omani ethnicity. Evidence of previous or current HBV infection was present in more than half of cirrhotic patients in Oman. This was determined by the presence of anti-HBc. HBV infection was more common among male cirrhotic patients compared to females whose most common aetiology was HCV.

There are multiple strengths and weaknesses to this study. Starting with the strengths, the study sample is relatively large. Patients were selected carefully using well-defined exclusion and inclusion criteria and the definition of cirrhosis was based on objective criteria. In addition, as 97.1% of patients were Omani, this eliminated the effect of geographical factors that might alter the progress of HBV infection to cirrhosis. One of these factors is HBV genotype. HBV genotypes have different geographical distribution as well as different pathogenicity in causing further hepatic disease (Kramvis et al., 2005).

Alcohol is a major co-factor for the development of cirrhosis. Due to the retrospective nature of data collection for this Omani study, a specific measurement of alcohol consumption was unavailable for this group of patients therefore; it was difficult to assess the synergetic effect of alcohol and HBV in the aetiology of cirrhosis. When combined with HBV infection, the natural course of the disease is affected negatively. The risk of cirrhosis increases by more than six times in HBsAg positive patients with history of high alcohol (Ikeda et al., 1998). In addition, the presence of anti-HBc alone with negative HBsAg status in patients with alcoholic cirrhosis was significantly associated with a more severe clinical profile (Zhang, 2013). Moreover, information regarding diabetes and family history of liver disease was incomplete and mostly missing. These are also thought to affect the prognosis of hepatitis B with regard to cirrhosis (see 2.3.5).

This study was also limited by the unknown status of HBV virology markers for some participants. For instance, HBsAg status was unknown for 9.79% of patients. This might underestimate the role of HBV infection in inducing cirrhosis among this studied cohort. Moreover, even though it was expected that the number of male patients would outweigh that of female patients, this number will be overestimated due to the unavailability of the

admission and discharge book from the red (females) ward for the year of 2007. These books were used to identify cirrhotic patients from the *Armed Forces Hospital*.

The male to female ratio in our study was found to be higher than one in all groups with viral hepatitis; however, the ratio was highest in patients currently infected with HBV (4.2), and lowest in patients with HCV infection (1.3). It has been suggested that females are more likely to clear HBV and develop antibodies against it compared to males, although the mechanism is unknown (Al-Faleh et al., 1992). Moreover, male gender has been identified as an independent risk factor for the development of cirrhosis in patients with chronic HBV. It is suggested that the antifibrogenic effect of oestrogen inhibits the activation of stellate cells and hence reduces the process of fibrosis (Fattovich et al., 2008). Male gender was also found to be a risk for developing HCC with an adjusted relative risk (ARR) of 2.1 (95 CI 1.3-3.3) and 3.6 (95% CI 2.4-5.3) in men compared to women.(McClune and Tong, 2010).

Throughout the world, the prevalence of HBV infection among cirrhotic patients is correlated with the endemicity of the virus in that area. Perz et al. estimated that the attributable fractions of cirrhosis due to infection with HBV ranged from 5% in regions with low endemicity to 57% in high endemicity regions (Perz et al., 2006). This attributable fraction was estimated to be 35% for states in the Eastern Mediterranean B, which includes Oman. If the same equation from Perz et al. is applied to our study cohort, the attributable fraction of cirrhosis due to HBV in Oman would be equal to 19.6%. This percentage is lower than that estimated by Perz et al.s' because their estimation was based on studies from Saudi Arabia and Tunisia that have different HBV prevalence to Oman. Saudi Arabia was considered to be of high endemicity for HBV (Abdo et al., 2012b), while Tunisia is placed in the upper threshold of intermediate endemicity (Ezzikouri et al., 2013). Other reasons for the different result may be due to the differences in the methodology of the studies. Data was collected prospectively in the studies from Saudi Arabia and Tunisia while retrospective data collection was conducted in this Omani study, and the accuracy of medical notes.

Past exposure to hepatitis B is determined by the resolution of HBsAg with or without the development of anti-HBs. It is associated with an increased mortality in patients without chronic liver disease (CLD) (aHR=1.29) (Jinjuvadia et al., 2013). We found in this study that almost one third 124 (29.6%) of our studied cohort had cleared past infection with HBV (HBsAg negative), of those, 77 were negative for any other viral markers (anti-HCV). When compared to a population of Omani blood donors, anti-HBc positivity was found in 20.5% of

the blood donors (Kaminski et al., 2006). The prevalence of anti-HBc is higher among cirrhotic patients than blood donors but the difference is not substantial. This can result from an over-estimation of the prevalence of anti-HBc in blood donors due to the use of one assay only as suggested by the authors. Conversely, HBV may not be the most important aetiology of cirrhosis in Oman and other factors such as HCV, alcohol and NASH need to be further evaluated.

Co-infection with HBV and HCV is associated with poorer prognosis. This study revealed that 12.6% of this sample of cirrhotic patients had HBV and HCV co-infection. Globally, it is estimated that 10-15% of CHB patients are co-infected with HCV (Fattovich et al., 2008). However, this was higher in this sample of patients as 58% of CHB patients were co-infected with HCV. This is because our definition of dual HCV and HBV infection was based on the positivity of HCV AB and anti-HBc (rather than HBsAg) (see 5.2, *Interpretation of virological markers*). Moreover, this sample is of cirrhotic patients whereas viral markers are expected to be higher than that of non-cirrhotic patients. The combined effect of HBV and HCV in causing HCC has been described in multiple international studies. A meta-analysis from China found that the odd ratio for developing HCC in patients positive for HBsAg and HCV AB (OR 35.7, 95% CI 26.2-48.5) was higher than in patients with HBsAg positive (OR 15.6, 95% CI 11.5-21.3) or HCV AB alone (OR 8.1, 95% CI 5.0-13.0) (Shi et al., 2005). Furthermore, dual infection with HBV and HCV accounts for 13.78% of HCC cases in China. In contrast, HCV positive patients with occult HBV infection (negative HBsAg, positive anti-HBc and positive HBV DNA) are associated with shorter survival rate ($p=0.03$), more frequent liver related deaths ($p<0.01$) and higher risk of developing HCC (Squadrito et al., 2013). That is because the mechanism in which HBV leads to HCC is maintained in the occult state.

This is the first study that has attempted to estimate the prevalence of HBV markers among patients diagnosed with cirrhosis in Oman. This is important because Oman is a country of intermediate endemicity for hepatitis B with an estimated prevalence of HBV infection of 2%-7% in the total population. However, there has not been any research done in Oman on the sequelae of hepatitis B such as cirrhosis and HCC. Such estimation would outline the social and economic burden of hepatitis B in Oman. In view of this, prospective studies which look at the outcome of HBV infection in Oman need to be conducted in the future. These studies will help in measuring the real extent of the problem as well as evaluating the

role of different exposures (alcohol, metabolic syndrome, and co-infection with other viruses such as HCV, HDV and HIV) to the outcome of the disease.

Prevention of HBV related complications can be achieved by primary, secondary and tertiary preventive strategies. Primary prevention with HBV vaccine is currently the best and most efficient preventive measure to reduce HBV related cirrhosis. The vaccine has been available since 1982. In Oman the hepatitis B vaccine was introduced Expanded Program Immunization in August 1990 with a reported coverage rate reaching more than 95% in 2005. It was also accompanied with catch-up campaigns to vaccinate school children who were born before that date and high risk groups. However, there is a time lag before appreciating the preventive effectiveness of the vaccine in reducing the burden of HBV-related hepatic cirrhosis and HCC. In our studied cohort, a very low fraction of patients had been vaccinated against HBV (5%) compared to more than a third (34%) being non-immune. We concluded from objective two of this thesis that most of HBV infection was acquired at a young age, with less frequent late horizontal transmission, so it may seem that immunizing older patients is not cost effective.

For at risk older individuals, a more selective policy is needed. Superimposed HBV infection in patients with CLD is associated with poorer outcomes when compared to the general population. Therefore, due to the high prevalence of HBV markers in patients with CLD, Lau and Hewlett recommended the pre-screening of CLD patients for HBsAg and anti-HBs, then vaccinating those negative for these markers will reduce the burden of the disease (Lau and Hewlett, 2005). As patients with CLD respond differently to the vaccine, Lau and Hewlett also recommended a post vaccination testing to assess the efficiency of the vaccine. In cirrhotic patients, the response was found to be dependent on the aetiology of cirrhosis, the severity of the disease and the age of the patient (Roni et al., 2013). Immunogenicity of the HBV vaccine was better in patients with HCV related cirrhosis compared to alcohol related cirrhosis with a less severe stage of the disease, and in patients younger than 50 years.

Secondary prevention of HBV related complications can be achieved with the use of anti-viral therapy in patients chronically infected with HBV before the introduction of the vaccine. These drugs have been found to be effective in reducing HBV morbidity and mortality (see 2.3.4). In Oman, treatment with lamivudine showed normalization of (ALT) in 81.8% of patients and reduced HBV DNA levels in 45% of patients (Dip et al., 2003).

Finally, once cirrhosis is established, tertiary prevention to avoid decompensating of cirrhosis and early detection of HCC have been developed. This can be achieved by treating HBV cirrhotic patients with available anti-viral therapy, and screening them for HCC. It was believed in the past that severe fibrosis of the liver in cirrhotic patients was irreversible. However, randomized controlled trials demonstrated the effectiveness of NUCs in reducing fibrosis and decompensation, hence, decreasing the need of liver transplant (Marcellin et al., 2013). Treatment with these drugs is found to be safe and well tolerated. As a result, current guidelines indicate the treatment of patients with compensated cirrhosis when HBV DNA levels are higher than 2000 IU/mL regardless of ALT levels. On the other hand, patients with decompensated cirrhosis are recommended for treatment regardless of ALT and HBV DNA levels (Mutimer and Lok, 2012).

Hepatocellular carcinoma is a major public health problem. It is the third most common cause of death worldwide, accounting for more than 600,000 deaths a year (Dhanasekaran et al., 2012). Fortunately, unlike many other types of cancer, the predisposing factors are well recognized such as HBV, HCV and aflatoxins. HBV is estimated to account for 53% of HCC cases worldwide (Perz et al., 2006), with 80% occurring in cirrhotic patients (El-Serag, 2011). This explains the highest incidence of HCC in areas where HBV is prevalent.

Knowing the risk factors for developing HCC helps in identifying high risk groups who should be under surveillance programs, with the assumption that early diagnosis leads to better treatment outcome. The *American Association for the Study of Liver Disease* and the *European Association for the Study of Liver Disease* recommend screening all cirrhotic patients, carriers for HBV, Asian males ≥ 40 years, Asian females ≥ 50 years and patients with family history of HCC every 6-12 months (Bruix and Sherman, 2005) (2012a). This makes most of this group of Omani patients eligible for HCC screening. The tests most commonly used for surveillance purposes are US and alpha-fetoprotein (AFP). US is a non-invasive test with no risk of radiation. It has been shown that US is effective in detecting HCC before clinical presentation; however, the efficacy is reduced in detecting early stages of HCC. Moreover, identifying small tumours is more difficult with underlying cirrhosis. AFP is a tumour marker for HCC. An AFP value of more than 200 or 400 ng/ml was found to be indicative of HCC with a 72% sensitivity, 89% specificity (Butt et al., 2012). Regardless, AFP is mainly used as a diagnostic rather than a surveillance test due to its suboptimal performance. This is because the levels of AFP are affected by the underlying disease and AFP is not raised in a significant proportion of tumours. There are several treatments of HCC

available depending on the stage of the tumour. These include surgical resection, transplantation, and locoregional therapy (Dhanasekaran et al., 2012).

In conclusion, HBV markers seemed to be common among cirrhotic patients in Oman where more than half of the patients had evidence of past or present HBV infection. Most patients were of older age and male sex. This group of patients is at high risk of developing HCC and regular screening will aid in reducing the burden of the disease in Oman. Further research is required to assess the role of other exposures in the progress of hepatitis B to cirrhosis in Oman.

6 IMPLICATIONS OF THE STUDY FINDINGS

This work was conducted to expand our understanding of hepatitis B in Oman in two major domains. These are: the risk factors for HBV transmission in Omani patients and the contribution of the virus to liver cirrhosis. A number of implications can be derived from the findings of this study which are discussed below.

In order to deal with any public health problem, the magnitude of the disease should be known. The estimated endemicity of hepatitis B in Oman is based on WHO calculations, while surveillance system shows a marked underestimation of the real burden. Therefore, a population-based study should be conducted to estimate the real prevalence of hepatitis B in Oman. Moreover, enhancing the surveillance of hepatitis B can be done in many ways. Firstly, as notifying HBsAg patients may be time consuming, trained staff should be available in all health centres to report the cases to the MoH using electronic notification methods. In addition, the civil number of patients should be collected to ensure the elimination of any duplicate cases.

Controlling the transmission of hepatitis B in Oman can be achieved by identifying the risk factors associated with the transmission. In our study, we found that intrafamilial contact with hepatitis B positive patients and behavioural risks to be prevalent among Omani adults positive for HBsAg. Despite the effectiveness of universal neonatal vaccination in preventing vertical transmission of hepatitis B, utilising available screening programs would further improve the control of hepatitis B. Antenatal screening of all pregnant women should be implemented in MoH institutes, and greater focus on contacts screening is needed. Moreover, further evaluation of the impact of practices such as piercings and barber shaving is recommended.

Chronic infection with hepatitis B is associated with the development of cirrhosis. We concluded from our study that more than half of the cirrhotic patients had a history of HBV infection. Anti-viral treatment of cirrhotic patients is needed to reduce risk of decompensation. Screening for HCC could further reduce the morbidity and mortality associated with hepatitis B. Further studies are needed to evaluate the effect of other exposures such as alcohol and co-infection with other viruses on the prognosis of CHB.

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8 Appendix

Hepatitis B Risk factors Questionnaire

Hospital:	Date:
ID:	Dob:
Gender:	Marital status:
Occupation:	Educational level:
Nationality:	Region:

Date and place of diagnosis with HBV (e.g. blood bank, pregnancy screening test):
Do you know why have you been referred to this hospital?
Did you know about hepatitis B before you have been diagnosed with it?
vaccination details (place and date):

Patients' medical history	0	1	≥2
Have you ever been hospitalized?			
Have you ever had any major surgery (e.g. caesarian birth, appendectomy)			
Please Specify surgery, place where conducted and date:			
Have you ever had any organ transplantation (liver or kidney)			
Please Specify surgery, place where conducted and date:			
Have you ever had an endoscopy?			
Please Specify surgery, place where conducted and date:			
Have you ever received any blood transfusion?			
Please Specify surgery, place where conducted and date:			
Have you ever been on dialysis?			
Do you have thalassemia or haemophilia?			
Have you ever been on chemotherapy treatment?			
Have you ever been on			

immunosuppressive medications?			
Have you ever had any major dental treatment?			

Patients' Social history	0	1	≥2
Do you have any tattoos?			
Do you have any piercings in your body?			
Where have you had it done?			
Have you ever been treated with phlebotomy (traditional)?			
Have you ever been treated with Wasam (cautery)?			
Have you ever had acupuncture?			
How often do you shave with a barber?			
Do you use syringes for other than medical reasons?			

Smoking history		Alcohol intake history	
Sexual activity		Circumcision history	

Is there any family history of HBV?		Please Specify relationship:	
Do you live with anyone who is diagnosed with HBV?		Please Specify relationship:	
Mothers' history of HBV			
Do you live with anyone who is diagnosed with any type liver diseases		Please Specify relationship:	

